The Era of New Pharmacology 101

LTC Peter Strube

DNAP CRNA MSNA APNP ARNP MBA(s)
Associate Professor Saint Mary’s University
Assistant Professor Rosalind Franklin University
Associate Academic Faculty, University of Wisconsin Oshkosh
Why is the patient having a panic attack?

It was just a MAC case .... “crazy patient” or was it something I did?
What IV Solution to You Choose?

NS or LR? (137 meq)

Panic attacks... oh boy?

“Lactate infusions commonly induce feeling of anxiety, and few cases of panic attack have been reported”

Package insert
Cauda Equina Syndrome

Is a rare condition but has serious consequences if not treated promptly. It is most often caused by a large disc herniation in the lower back that compresses the nerve roots at the end of the spinal cord that causes bowel and bladder dysfunction.
Disclaimer; Chronic Cough
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.
Patient Satisfaction?

LAST TIME I TRUSTED YOU

I WOKE UP WITHOUT MY BALLS
The Power of Words

New Drugs and new ways of approaching patients...... CHOOSE WISELY!

Do you have any pain? verse how do you feel?
Crazy?

Diamorphine Hydrochloride
100mg
for Injection BP
5 ampoules

Ecstasy Helps Treat PTSD Patients, Trial Finds

Desoxyn®
(methamphetamine hydrochloride tablets, USP)

NDC 55292-102-01 100 Tablets

Each tablet contains 5 mg.
methamphetamine hydrochloride.
See package insert for full
prescribing information.
Store below 86°F (30°C).
Dispense in a USP tight,
light-resistant container.
Do not accept if seal over bottle
opening is broken or missing.
Manufactured by: AbbVie LTD
For: Recordati Rare Diseases Inc.
Lebanon, NJ 08833, U.S.A.

Ancient drug yielding new use
‘Magic mushrooms’ being tested by UW as option
for cancer patients, others
Xofluza, Flu Drug That Kills Virus in 24 Hours, Approved in Japan

Flu season: Xofluza can kill flu virus in 24 hours with a single dose – TomoNews

Shionogi: XOFLUZA (Baloxavir Marboxil) Tablets 10mg/20mg Approved for the Treatment of Influenza Types A and B in Japan

02/22/2018 | 10:12pm EST

XOFLUZATM (Baloxavir Marboxil) Tablets 10mg/20mg Approved for the Treatment of Influenza Types A and B in Japan
MRSA INFECTION
METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

Cutaneous abscess caused by MRSA
### 5th Generation Cephalosporins

<table>
<thead>
<tr>
<th>Specific antibiotic</th>
<th>Ceftaroline</th>
</tr>
</thead>
</table>
| Spectrum            | Gm positives, including MRSA!  
Gm negative respiratory pathogens, enteric bacilli (similar to cefotaxime), NOT active against *Pseudomonas*, NOT stable to ESBL’s |
| Uses                | MRSA infections  
Nosocomial infection, empiric therapy where MRSA is a concern |

<table>
<thead>
<tr>
<th>Drug</th>
<th>Administration</th>
<th>Attributes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefdinir</td>
<td>Oral</td>
<td>Very important development</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stable against most TEM &amp; SHV beta lactamases</td>
</tr>
<tr>
<td>Cefixime</td>
<td>Oral</td>
<td>Very potent against GNB</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>Parenteral</td>
<td>Some had excellent activity against <em>Pseudomonas</em></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Parenteral</td>
<td>Slightly less active than 1st</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Parenteral</td>
<td>Gen against GPC</td>
</tr>
<tr>
<td>Cefoperazone</td>
<td>Parenteral</td>
<td>Modest activity against anaerobes</td>
</tr>
</tbody>
</table>
Life Long Learning = Better Patient Care!

Tablets
Topamax®
(topiramate)

Sprinkles
TOP
15 mg
TOP
25 mg
400 mg of riboflavin, 65 mg of caffeine and 325 mg Tylenol


High-dose riboflavin treatment is efficacious in migraine prophylaxis: an open study in a tertiary care centre.
Boehnke C¹, Reuter U, Flach U, Schuh-Hofer S, Einhäupl KM, Arnold G.


Effectiveness of high-dose riboflavin in migraine prophylaxis. A randomized controlled trial.
Schoenen J¹, Jacqz J, Lenaerts M.


Riboflavin prophylaxis in pediatric and adolescent migraine.
Condó M³, Posar A, Arizzani A, Parmeggiani A.


Supplementation with Riboflavin (Vitamin B2) for Migraine Prophylaxis in Adults and Children: A Review.
Namazi N¹, Heshmati J², Tarighat-Esfaniani A³.
The next slide is a new pharmaceutical advertisement that has some rough language.

Close your ears if you don’t want to listen to a cutting edge pharmacology advertisement.

If you do listen, you will want a prescription, TRUST ME!
Disclaimer; this pharmaceutical add has some rough language, close your ears if you don’t want to listen to cutting edge pharmacology advertisement.

Last Chance....
Disclaimer; this pharmaceutical add has some rough language, close your ears if you don’t want to listen to cutting edge pharmacology advertisement.
In less than 5 years tapes were gone.
14-17 Years

KEEP CALM AND...

...ok, not THAT calm!
AFE – September 29, 2014 (presentation)
Dr. B Leighton, Cooper, Otto
(abstract fall 2013)

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
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 G8P043 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 13 units PRBC, 6 units FFP, 2 units platelets, 30 units 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 to 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
Propofol

The Pharmacodynamic Effects of a Lower-Lipid Emulsion of Propofol: A Comparison with the Standard Propofol Emulsion

Propofol in a Modified Cyclodextrin Formulation: First Human Study of Dose–Response with Emphasis on Injection Pain

Wallentine, Crystal B. MD*; Shimode, Noriko MD*; Egan, Talmage D. MD*; Pace, Nathan L. MD, MStat*

Anesthesiology & Analgesia: October 2011 - Volume 113 - Issue 4 - p 738–741

Propofol Cyclodextrin
IDD-D Propofol
Ampofol
Prodrug Aquavan

Aquavan

- A new water-soluble prodrug of propofol
- This prodrug is rapidly hydrolyzed by plasma alkaline phosphatases in the circulation to release free propofol.
- It has a slower onset but a similar recovery profile.
- does not produce injection site discomfort, a transient burning sensation has been reported in the perineal region following IV injection.

New Medications and Techniques in Ambulatory Anesthesia

M. Stephen Melton, MD; Karen C. Nielsen, MD; Marcy Tucker, MD, PhD; Stephen M. Klein, MD; Tong J. Gan, MD, MHS, FRCA, MB, FFARCS; Ed
Department of Anesthesiology, Duke University Medical Center, Box 3094, Durham, NC 27710, USA
Fospropofol (Lusedra)

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

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??
Fospropofol  -- Bad Chemistry

http://www.lusedra.com

Trade name: Lusedra

Packaged as 35 mg/mL

Dose is 6.5 mg/kg

Prodrug, is metabolized to propofol

Gained some popularity during propofol shortages
Life Long Learning = Better Patient Care!

300 mg Magnesium and 40 mg of Lidocaine

Clinical Therapeutics/Volume 38, Number 1, 2016

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

Jiehao Sun, MD; Riyong Zhou, MD; Wendong Lin, MD; Jiahao Zhou, MD; and Weijian Wang, MD

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

Ondansetron Pretreatment to Alleviate Pain on Propofol Injection: A Randomized, Controlled, Double-Blinded Study

Ambesh, Sushil P. MD; Dubey, Prakash K. MD; Sinha, Prabhat K. MD

Anesthesia & Analgesia: July 1999 - Volume 89 - Issue 1 - p 197-199
doi: 10.1213/00000539-199907000-00035
General Articles

Ondansetron Pretreatment Reduces Pain on Injection of Propofol

Hamid Zabedi, Anahid Maleki, and Gholamreza Rostami

Department of Anesthesiology, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran

Received: 7 Mar. 2011; Received in revised form: 2 Jul. 2011; Accepted: 30 Jul. 2011
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/curare and/or vecuronium or atracurium; and supplemental isoflurane) were evaluated in two double-blind US studies involving
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

Utilizes the ester design.

Broken down by nonspecific ester hydrolysis

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

Phaxan™: Intravenous Anaesthetic and Sedative

Phaxan™ is an intravenous general anaesthetic and sedative containing alphaxalone as the active pharmaceutical ingredient. Alphaxalone is a neuroactive steroid anaesthetic. It is a pregnanediolone with no endocrine hormonal activity. This water-insoluble drug was initially formulated using CremophorEL and marketed as Althesin® from 1972 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 CremophorEL.

Many subsequent attempts to make an aqueous formulations of neuroactive steroids suitable for human use have failed. Drawbridge Pharmaceuticals’ proprietary and patented formulation, Phaxan™, is a solution of alphaxalone 10mg/ml dissolved in 13% SBECO (7-sulfobutyl ether β-cyclodextrin): a molecule with a lipophilic cavity that enables drug dispersal in water for human use. The use of SBECO 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 CremophorEL. The properties of the new anaesthetic preparation:


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.
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.

**MOC-etomidate had half-life of 4.4 minutes versus more than 40 minutes for etomidate.**

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.
Etomidate-Lipuro 2mg/cc

Lipuro® inside - The innovative Etomidate-Lipuro is based on the original B. Braun Lipuro®-Technology, which uses an MCT/LCT lipid emulsions as the drug carrier system for the sedative agent etomidate
Does not contain antimicrobial preservations
Presentation: 10 ml glass ampoule

Etomidate Lipuro (Etomidate Injection, USP) is a sterile, nonpyrogenic solution. Each milliliter contains etomidate, 2 mg, propylene glycol 35% v/v. The pH is 6.0 (4.0 to 7.0).

It is intended for the induction of general anesthesia by intravenous injection.

The drug Etomidate Lipuro is chemically identified as (R)-(+)ethyl-1-(1-phenylethyl)-1H-imidazole-5-carboxylate and has the following structural formula:

More: https://www.sdrugs.com/
Ryanodex

The drug, an injectable suspension of dantrolene sodium

Eagle Pharmaceuticals, Ryanodex can be prepared and administered in less than one minute

The cost for a patient receiving Ryanodex treatment for a MH crisis (based off 2.5mg/kg in a 70kg patient) is $1,610 verses $700 with generic dantrolene.
Mivacurium is back!

Because minutes matter, in adults you may expect 15–20 minutes of neuromuscular blockade with the only short-acting nondepolarizing agent available.¹,²

¹Range in clinical trials with 0.15 mg/kg dose: 9–38 minutes.¹
2014 Lit review identified 15 cases of hypersensitivity reactions from sugammadex.
Cost of Sugammadex

- 70kg man
- 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
  - Neostigmine 5 mg and Robinol 1.0 mg = $300 - $400
  - 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??
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
During your procedure or surgery on ____________________________

you received medications that lower the effectiveness of birth control medications. You need to be aware of this if you are on any type of a hormonal contraceptive (birth control medication):

☐ Sugammadex (Bridion®) is a medicine that helps to speed up recovery from anesthesia (muscle relaxant) drugs patients receive during surgery. Sugammadex may decrease the effectiveness of your hormonal contraceptive (birth control) for up to 7 days.
  o Use a backup birth control method for up to 7 days after your procedure or surgery
  o Continue taking your hormonal contraceptive during this period

☐ Aprepitant (Emend®) is a medicine that prevents nausea. Aprepitant may decrease the effectiveness of your hormonal contraceptive (birth control) for up to 28 days.
  o Use a backup birth control method for up to 28 days after your procedure or surgery
Sugammadex

It is NOT the savior it is billed as...

You must use it correctly and reverse correctly. If you under reverse the patient will still be “floppy” and have residual paralysis...

Hence the same problem as before...

Recurarization after sugammadex following a prolonged rocuronium infusion for induced hypothermia

Tetsuya Murata, MD · Toshi Kubodera, MD · Masakazu Ohbayashi, MD · Kichiro Murase, MD, PhD · Yushi U. Adachi, MD, PhD · Naoyuki Matsuda, MD, PhD
Life Long Learning = Better Patient Care!

Recurarization

Reports range between 25-70%

Sugammadex: Importance of Monitoring and Appropriate Dosing

- Dosing is crucial and requires monitoring
- In a study conducted in Japan, Kotake and colleagues found that in the absence of monitoring (no peripheral nerve stimulators or neuromuscular monitors used), residual block can occur with sugammadex.

Continuous succinylcholine infusion and phase II block in short surgical procedures.

Chen YA¹, Fan SZ, Lee PC, Shi JJ, Tsai YC, Chang CL, Liu CC.

SUCCINYLCHOLINE DRIP DURING CRANIOTOMY

KENNETH HALL, M.D.; MAITLAND BALDWIN, M.D.; FORBES NORRIS, M.D.

Anesthesiology 1959, Vol.20, 65-70. doi:

Less than $1 for a gtt or $1000 for Roc and Sugammadex
Gantacurium  
Phase 2 complete  
Third generation of tetrahydroisoquinolinium

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

---

The multicenter, randomized, controlled, observer-blinded dose-response study was designed to evaluate the efficacy and safety of gantacurium chloride for injection in healthy adult patients undergoing endotracheal intubation prior to surgery under general anesthesia. The study enrolled 230 subjects with American Society of Anesthesiologists (ASA) physical status classification 1 and 2 (healthy or mild systemic disease), who were given gantacurium, succinylcholine or placebo. The study met its primary outcome endpoint, achieving greater than 90 percent acceptable intubations at 60 seconds after injection. Gantacurium was generally well tolerated and no serious adverse events were observed.
Gantacurium

Dose: 0.5 mg/kg

Fast acting with short duration

Key is: NO histamine release!

The Efficacy and Safety of Gantacurium Chloride for Injection in Tracheal Intubation in Healthy Adult Patients Undergoing Surgery Under General Anesthesia


Novel drug development for neuromuscular blockade.
Prabhakar A¹, Kaye AD¹, Wyche MQ¹, Salinas OJ¹, Mancuso K¹, Urman RD².
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!
Cysteine

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
Calabadion: A new agent to reverse the effects of benzylisoquinoline and steroidal neuromuscular-blocking agents.

Hoffmann U¹, Grosse-Sundrup M, Eikermann-Haerter K, Zaremba S, Ayata C, Zhang B, Ma D, Isaacs L, Eikermann M.
Comparative Effectiveness of Calabadion and Sugammadex to Reverse Non-depolarizing Neuromuscular-blocking Agents


Calabadion: A New Agent to Reverse the Effects of Benzyldisoquinoline and Steroidal Neuromuscular-blocking Agents

Ulrike Hoffmann, M.D.; Martina Grosse-Sundrup, M.D.; Katharina Eikermann-Haerter, M.D.; Sebastina Zaremba, M.D.; Cenk Ayata, M.D.; Ben Zhang, B.S.; Da Ma, Ph.D.; Lyle Isaacs, Ph.D.; Matthias Eikermann, M.D., Ph.D.

Calabadion: A New Agent to Reverse the Effects of Benzyldisoquinoline and Steroidal Neuromuscular-blocking Agents.
Hypotensive Thought Pattern

Methylene blue?

Vasopressin?

Glucagon?
Methylene Blue

This is an age-old drug; traditionally used for Methemoglobinemia and as a tissue marker.

Has been used with liver transplant for hypotension.

Reports of being used for patients on ACE inhibitors for refractory hypotension.
Hemodynamic Effects of Methylene Blue

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
Glucagon

Glucagon enhances the formation of cAMP.

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

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
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.
Shortage

Reason for the Shortage American Regent discontinued vasopressin injection in early 2015.

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

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

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

Antidote: Entereg (Alvimopan)
We Must Start to Think Differently!

Multi-Modal Synergy
Pre-emptive
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.

Fentanyl Patch

Transdermal Patch

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

BUCCAL TABLET; BUCCAL SOLUBLE FILM; SUBLINGUAL TABLETS; NASAL SPRAY; SUBLINGUAL SPRAY
Life Long Learning = Better Patient Care!

Fentanyl

Insys Therapeutics, Inc.

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

Capsaicin (Zostrix)

Is a new Receptor Born? **TRPV 1**

Selectively stimulates unmyelinated C fibers afferent neurons and cause release of substance P

This continued release leads to depletion of substance P and decrease in pain


TRPV1 agonism inhibits endothelial cell inflammation via activation of eNOS/NO pathway.

Wang Y¹, Cui L², Xu H³, Liu S², Zhu F², Yan F², Shen S², Zhu M⁴.


Quantitative Thermal Testing Profiles as a Predictor of Treatment Response to Topical Capsaicin in Patients with Localized Neuropathic Pain.

Serrano A¹, Torres D², Veciana M³, Caro G¹, Montero J¹, Mayoral V¹.


Warming up to New Possibilities with the Capsaicin Receptor TRPV1: mTOR, AMPK, and Erythropoietin.

Malese K¹.
An additional product candidate under development is Fadolmidine [Fado] which also belongs to the alpha-2 adrenergic agonist receptor class.

Fadolmidine is similar to Dex and different from clonidine in that it is a full agonist of all subtypes of alpha-2 adrenoreceptor.
Intuniv decreases certain nerve signals from the brain to the blood vessels and the heart. This causes the blood vessels to relax so that blood flows more easily and slows the heart rate. These effects help to lower blood pressure. The drug lowers blood pressure and heart rate, thereby suppressing the body's “fight or flight response” by decreasing that activity of part of the brain known as vasomotor center. Many users of Intuniv experience sedation or drowsiness.

Guanfacine is a highly selective agonist of the $\alpha_{2A}$ adrenergic receptor, with negligible affinity for any other receptor.
Tenax --- Intuniv
Alpha-2 agonist;
The efficacy of guanfacine in reducing perioperative hemodynamic changes and volatile anesthetic requirement

Kahoru Nishina, MD*, Katsuya Mikawa, MD†, Nobuhiro Maekawa, MD‡, Hidefumi Obara, MD§
Department of Anesthesiology, Kobe University School of Medicine, Kobe 650, Japan
* Research Fellow.
† Assistant Professor.
§ Professor and Chairman.
Tranexamic Acid

FIBRINOLYSIS:

Plasminogen → Plasmin → dissolves Clot

Release of:
- t-PA (fibrinolysis)
- thrombomodulin (blocks coagulation cascade)
Tranexamic Acid

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
Antidote to Thrombin Inhibitors

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.
## Coagulation Factors

<table>
<thead>
<tr>
<th>FACTORS</th>
<th>PLASMA t ½ (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen (I)</td>
<td>72-120</td>
</tr>
<tr>
<td>Prothrombin (II)</td>
<td><strong>60-70</strong></td>
</tr>
<tr>
<td>V</td>
<td>12-16</td>
</tr>
<tr>
<td>VII</td>
<td><strong>3-6</strong></td>
</tr>
<tr>
<td>VIII</td>
<td>8-12</td>
</tr>
<tr>
<td>IX</td>
<td><strong>18-24</strong></td>
</tr>
<tr>
<td>X</td>
<td><strong>30-40</strong></td>
</tr>
</tbody>
</table>

### Vitamin-K dependent factors (II, VII, IX, X)(S and C)

<table>
<thead>
<tr>
<th>FACTORS</th>
<th>PLASMA t ½ (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XI</td>
<td>52</td>
</tr>
<tr>
<td>XII</td>
<td>60</td>
</tr>
<tr>
<td>Protein C</td>
<td><strong>6</strong></td>
</tr>
<tr>
<td>Protein S (total)</td>
<td><strong>42</strong></td>
</tr>
<tr>
<td>Tissue factor</td>
<td>--</td>
</tr>
<tr>
<td>Thrombomodulin</td>
<td>--</td>
</tr>
<tr>
<td>Antithrombin</td>
<td>72</td>
</tr>
</tbody>
</table>
Four-Prothrombin Complex Concentrates

Vitamin K-dependent coagulation factors plus antithrombotic Proteins C and S

Factors

II VII IX X

Antithrombotic Proteins

C S

- Nonactivated
- Contains antithrombin III and heparin
- Administer concurrently with vitamin K
- 36-month room-temperature storage prior to reconstitution
Kcentra—http://www.kcentra.com/

Kcentra®, Prothrombin Complex Concentrate (Human), is a blood coagulation factor replacement product indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA—eg, warfarin) therapy in adult patients with acute major bleeding or the need for urgent surgery or other invasive procedure. Kcentra is for intravenous use only.

A single dose of Kcentra is determined by the patient’s pretreatment INR and weight.

<table>
<thead>
<tr>
<th>Pretreatment INR</th>
<th>2–&lt;4</th>
<th>4–6</th>
<th>&gt;6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose of Kcentra</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(units of Factor IX)/kg body weight</td>
<td>25</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>Maximum dose*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(units of Factor IX)</td>
<td>Not to exceed 2500</td>
<td>Not to exceed 3500</td>
<td>Not to exceed 5000</td>
</tr>
</tbody>
</table>

10mg/500 units Vit K

$1.27/unit
Life Long Learning = Better Patient Care!

http://www.anesthesiainsights.com/mobile-app-reviews/

ASRA applications are $3.99
Life Long Learning = Better Patient Care!

Lets look at it with new drugs and differently

Postoperative Nausea and Vomiting
Anesthetic-specific risk factors

Use of nitrous oxide??

Use of neostigmine to reverse NMB ??


Is it true?
Is it true? Neostigmine

Meta-analysis by Cheung, Sessler, Apfel
933 patients in 10 studies
Extracted data on PON and POV for early, delayed, and overall postoperative periods

**Neostigmine was not associated w/ a significant ↑ in PON or POV**

- Combination of neostigmine with either atropine or glycopyrrolate did not significantly ↑ incidence of PON or POV (0-24 h)
- No ↑ vomiting w/ ↑ dose of neostigmine

Nitrous

Omitting nitrous oxide in general anesthesia: Meta-analysis of intraoperative awareness and postoperative emesis in randomized controlled trials.

British Journal Anaesthesia 76:186-93, 1996. Nitrous oxide adds to the number of patients who have postoperative vomiting only if the baseline risk of vomiting is above average.

The average risk groups experience no increase in PONV when nitrous oxide is used.
Oxygen

Hypoxia triggers cortical afferents which triggers the vomiting center which leads to the act of vomiting.

One specific study showed a decreased rate of PONV.

A second study trying to prove the first could not either prove or disprove the first study.

Increased O2 levels (less than 80%) in orthopedics have been shown to decrease infection rates in total joints.

Interesting thoughts?
Supplemental perioperative oxygen improves postop outcomes

FiO₂ of 0.8 doubles subcut O₂ tension & halves postop wound infection rate

Supplemental O₂ ↓ PONV after laparoscopies & laparotomies

*Curr Opin Anesthesiol* 2006;19:11-18
Dosing of Ephedrine

A study by Rothenberg et al. (1991) showed that ephedrine 0.5 mg/kg IM has an antiemetic effect in patients undergoing outpatient laparoscopy with general anesthesia.
20-30 mg Propofol

Propofol, in small doses (20 mg as needed), can be used for rescue therapy for patients in the direct care environment, for example, PACU, and has been found as effective as ondansetron.


Propofol

The benefit of a small dose propofol infusion (bolus of 1 mg/kg followed by an infusion at 20 mcg/kg/min), either by itself or in combination with other antiemetics, has been shown to reduce PONV.


Erdem AF, Yoruk O, Silbir F, Alici HA, Cesur M, Dogan N, Aktan B, Sutbeyaz Y. Tropisetron plus sub hypnotic propofol infusion is more effective than tropisetron alone for the pre-vention of vomiting in children after tonsillectomy. Anaesth Intensive Care 2009;37:54–9
October 20, 2009 (New Orleans, Louisiana) — The simple intravenous (IV) administration of dextrose following surgery significantly reduces the occurrence of postoperative nausea and vomiting (PONV) and the need for antiemetic medication in the postoperative anesthesia care unit (PACU), investigators reported here at the American Society of Anesthesiologists 2009 Annual Meeting.
Nicotine??

Nicotine agonists;

Nicotine nasal spray dose of 3 mg versus NS nasal spray placebo during closure


Randomised trial of intranasal nicotine and postoperative pain, nausea and vomiting in non-smoking women.

Ginger administered prior to induction of anesthesia can be prophylactic for PONV (1 gram) TOXIC is greater than 2mg/kg/day
Palonosetron (Aloxi) -- PDNV

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.

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
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/curare and/or vecuronium or atracurium; and supplemental isoflurane) were evaluated in two double-blind US studies involving
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
Versed

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.
The last 30 Minutes Versed


Conclusion, the results of this study indicated that for patients undergoing surgery, midazolam 2 mg given intravenously 30 minutes before the end of surgery was effective in decreasing the incidence of PONV without increasing recovery time and the level of sedation.
Olanzapine as an Antiemetic:

Atypical antipsychotic that belongs to the thienobenzodiazepine class.

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

Most Studies looked at it as compared to Zofran.................
Doxylamine – Pyridoxine (Diclegis)

Original marketed as Bendectin (1956)

Also called Duchesnay

Combination of Vitamin B6 (10 mg) and Antihistamine (10 mg)
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#
Emend (Aprepitant) PDNV

A new class of antiemetic's is born -- NK-1 receptor antagonists

Does not interfere with other antiemetic’s

No dosage adjustments for hepatic or renal compromise

Does not effect QT segments

Expensive single 80mg dose is $125

Decreases efficacy of hormonal contraceptives

Two additional NK-1 Drugs: Casopitant, Rolapitant
Birth Control Drug Interaction with Sugammadex (Bridion®) and/or Aprepitant (Emend®): Information for Female Surgery Patients

During your procedure or surgery on ____________________________

you received medications that lower the effectiveness of birth control medications. You need to be aware of this if you are on any type of a hormonal contraceptive (birth control medication):

☐ Sugammadex (Bridion®) is a medicine that helps to speed up recovery from anesthesia (muscle relaxant) drugs patients receive during surgery. Sugammadex may decrease the effectiveness of your hormonal contraceptive (birth control) for up to 7 days.
   o Use a backup birth control method for up to 7 days after your procedure or surgery
   o Continue taking your hormonal contraceptive during this period

Aprepitant (Emend®) is a medicine that prevents nausea. Aprepitant may decrease the effectiveness of your hormonal contraceptive (birth control) for up to 28 days.
   o Use a backup birth control method for up to 28 days after your procedure or surgery
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.
Cannabinoids

- Salivex
- Ajulemic acid
- Nabilone
- Marinol
- Cannadur
- Cannabis

As of 2013; 23 controlled studies looking at Cannabinoids for pain management
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.
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.)
It is OK......

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†; Szokol, Joseph W. MD†; Avram, Michael J. PhD†; Greenberg, Steven B. MD†; Shear, Torin MD†; Vender, Jeffery S. MD†; Gray, Jayla BA†; Landry, Elizabeth BA†

Anesthesia & Analgesia:
June 2014 - Volume 118 - Issue 6 - p 1204–1212
doi: 10.1213/ANE.0b013e3182a53981
Ambulatory Anesthesiology: Research Report
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.


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Special Letter to the Editor:

Rivastigmine (Exelon) Patch May Complicate Use of Neuromuscular Blocking Drugs

Today, many patients with Alzheimer’s disease present for surgery. A high index of suspicion for Achl from an oral or transdermal source should be suspected and sought. If time permits, a rivastigmine patch should be removed at least 24 hours before any anticipated general anesthetic, but the effects of residual Achl should still be anticipated and tracked with neuromuscular monitoring. Other considerations for patients on Achl include a preference for regional anesthesia or the avoidance of NMBs if possible.

Interactions:

Antagonizes anticholinergics. May potentiate succinylcholine-type muscle relaxants, other cholinesterase inhibitors, cholinergic agonists. Monitor for GI bleed with NSAIDs. Concomitant metoclopramide, beta-blockers: not recommended.
Indocyanine Green

IC green is used for determining cardiac output, hepatic function and liver blood flow, and for ophthalmic angiography.

Following intravenous injection, indocyanine green is rapidly bound to plasma protein, of which albumin is the principle carrier (95%).

Indocyanine green is taken up from the plasma almost exclusively by the hepatic parenchymal cells and is secreted entirely into the bile.

IC green can be used during plastic surgery to aid in the assessment of blood flow to grafts/flaps.
Neurosurgical Applications for Indocyanine Green

Intraoperative use of indocyanine green fluorescence videography for resection of a spinal cord hemangioblastoma.
Hwang SW, Malek AM, Schapiro R, Wu JK.
Department of Neurosurgery, Tufts Medical Center, Boston, Massachusetts, USA. stevenhwang@hotmail.com

IC-green has been utilized by neurosurgeons to aid in the management of various pathologies, including intracerebral aneurysms and spinal cord tumors.

In these instances, the neurosurgeon will request that the anesthesia provider administer the IC-green intravenously.
Spy Elite

Inject IC-Green; give 10 cc of 2.5 mg/cc at least 30 minutes before procedure.
Exparel

EXPARSEL 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.
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 infiltrated 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 blood concentrations might result, and cardiac conductivity and excitability may be depressed, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest.
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

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

RE: NDA # 022496
EXPARCEL® (bupivacaine liposome injectable suspension)
MA# 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

Life Long Learning = Better Patient Care!
POSIMIR® (SABER®-Bupivacaine)

Overview

POSIMIR is an investigational nonopioid analgesic being evaluated for its ability to provide 3 days of continuous local pain relief after surgery. Intended for administration just once at the close of surgery, POSIMIR may be instilled directly into the surgical incision(s) with a blunt-tipped applicator or injected into targeted anatomic spaces under endoscopic guidance. Once placed, clinical and nonclinical studies have shown it to form a biodegradable depot that releases bupivacaine directly to the surgical site at a stable rate for 72 hours.

Based on DURECT’s proprietary SABER technology, POSIMIR is anticipated to play a central role in modern multimodal postoperative pain management protocols. It has been studied in open, laparoscopic, and arthroscopic surgeries. It has not been approved by the FDA for marketing in the U.S. for any indication.

SABER® PLATFORM

SABER = Sucrose acetate isobutyrate extended release
Combined local anesthetics dosage calculation

POSTED ON 03/02/2012 BY UCSFREDO

How should we calculate the maximum dosage of the local anesthetics, if the more than one type of anesthetic agents are to be administered? For example, the administration of 2% lidocaine together with 4% articaine?

In part of our Lit Review on ‘Essentials of Local Anesthetic Pharmacology’ by Becker et al in 2006, the dosage calculation for combined local anesthetic agents was mentioned. The paper suggests that the ‘additive’ percent of maximum dosage of each local anesthetic agent should be calculated.

Basically it means that if half (50%) of the maximum dosage of the first agent has been used, no more than 50% of the maximum dosage the second agent should be administered. Of course, in this case, if the first agent dosage was maxed out (100%), for safety, the second agent should not be administered at all (0%). This calculation will be particularly helpful in a-difficult-to-anesthetize patient who may require more than one type of local anesthetics.
FDA Drug Shortages

Current and Resolved Drug Shortages and Discontinuations Reported to FDA

Search by Generic Name or Active Ingredient: Enter at least three characters

Current/Resolved Shortages Discontinuations Therapeutic Categories New and Updated

› Analgesia/Addiction

› Anesthesia
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0.05mg/kg dose was 25%
0.2mg/kg, 8.3%
0.4mg/kg, 5.4%.
Woman badly burned after farting during surgery

By Ian Horswill, News.com.au

November 1, 2016 | 9:03am | Updated

A patient who passed gas during an operation was badly burned when the fart ignited a laser being used in the surgery, a hospital report states.

The unnamed woman, in her 30s, was undergoing surgery at Tokyo Medical University Hospital which involved a laser being applied to her cervix.
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.
Can I be excused?  
... my brain is full!
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Questions?