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

Certified Registered Nurse Anesthetist

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.

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Surgery Before Anesthesia and Pharmacology

Mural of Dr. Villandet, Hôtel de Dieu, Paris. A

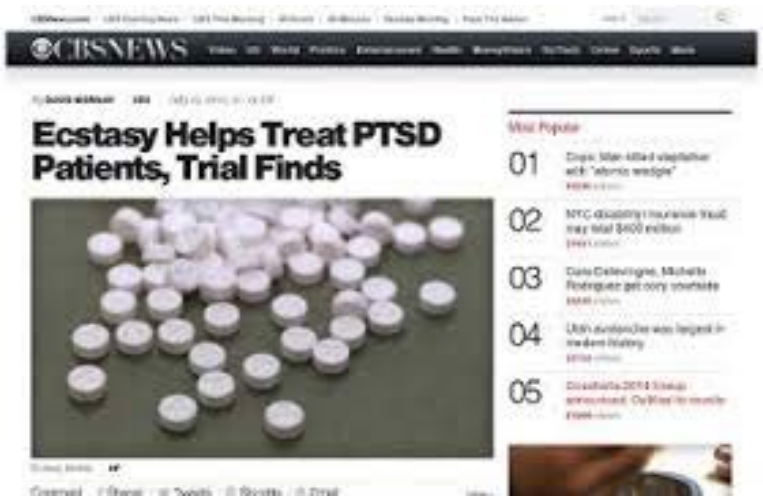
From *Behind the Doctor*, by Logan Clendenning, published by Alfred A. Knopf. B

From *Devils, Drugs and Doctors*, by Howard W. Haggard, M.D., published by Harper and Brothers. C

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.

Crazy?



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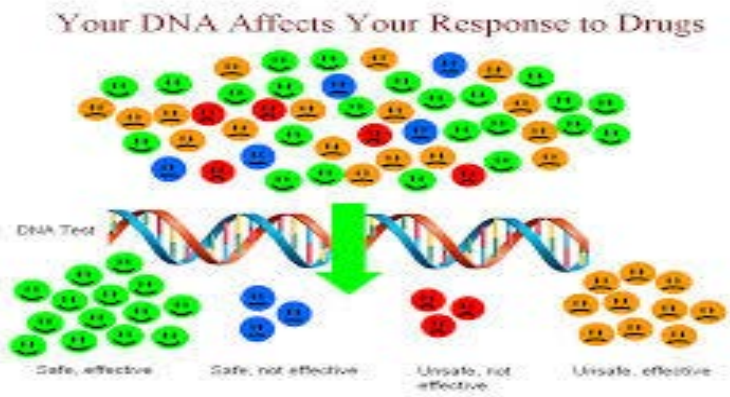
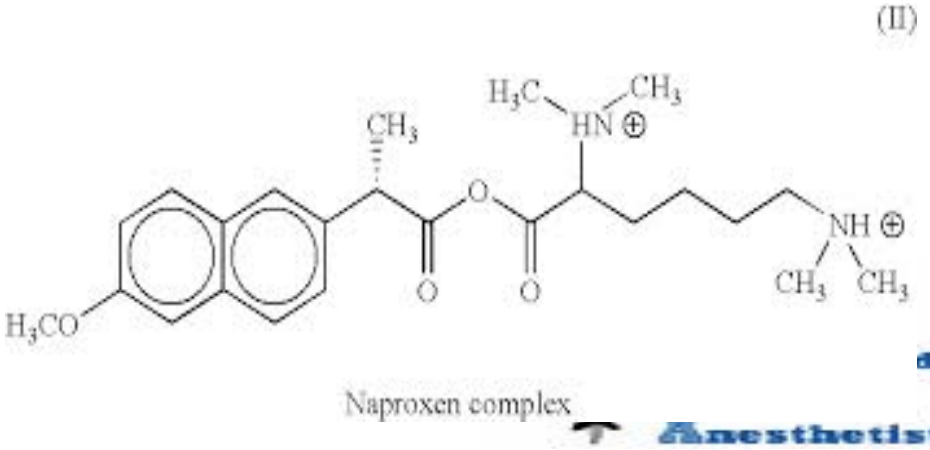
Think outside the BOX—
Think Differently!

Old Drugs, New Ways

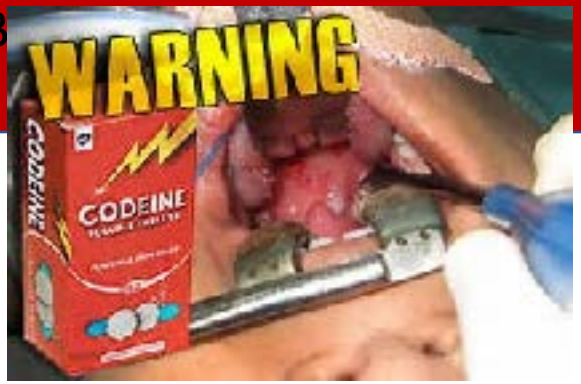
New Drugs, Old Battles!

Pharmacogenetics----Micron Technology





We Must Start to Think Differently!



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.

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Think outside the BOX

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

Multimodal

Synergy

Preemptive

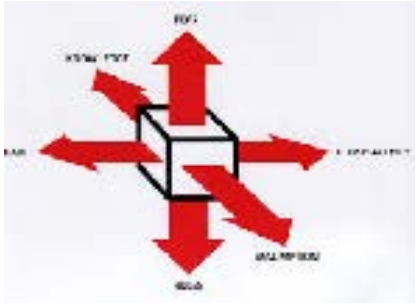
Standard, Policy, Guideline, Suggestion???

Zofran

Food and Drug Administration MedWatch

FDA Alerts!

FDA and Codeine?



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; opicid: 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 554 patients. ZOFRAN 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 8. Prevention of Postoperative Nausea and Vomiting in Adult Patients

	Ondansetron 4 mg I.V.	Placebo	*P* Value
Study 1			
Emetic episodes: Number of patients Treatment response over 24-h postoperative period	136	139	
0 Emetic episodes	103 (76%)	64 (46%)	<0.001
1 Emetic episode	13 (10%)	17 (12%)	
More than 1 emetic episode/rescued	20 (15%)	58 (42%)	
Nausea assessments: Number of patients No nausea over 24-h postoperative period	134 56 (42%)	136 39 (29%)	
Study 2			
Emetic episodes:			


25
100
200
TOP
15 mg
TOP
25 mg
Tablets
Sprinkles
Topamax®
(topiramate)

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

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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.

Marazziti D, Dell'Osso B, Baroni S, Mungai F, Catena M, Rucci P, Albanese F, Giannaccini G, Betti L, Fabbrini L, Italiani P, Del Debbio A, Lucacchini A, Dell'Osso L (2006). "A relationship between oxytocin and anxiety of romantic attachment". Clinical Practice and Epidemiology in Mental Health **2** (1): 28. doi:10.1186/1745-0179-2-28. PMC 1621060. PMID 17034623.

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

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 MD[1] ; Maryann P Otto MD[2]; Barbara L Leighton MD[3]

Washington University in Saint Louis[1] ; Washington University in Saint Louis[2]; Washington University in Saint Louis[3]

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.

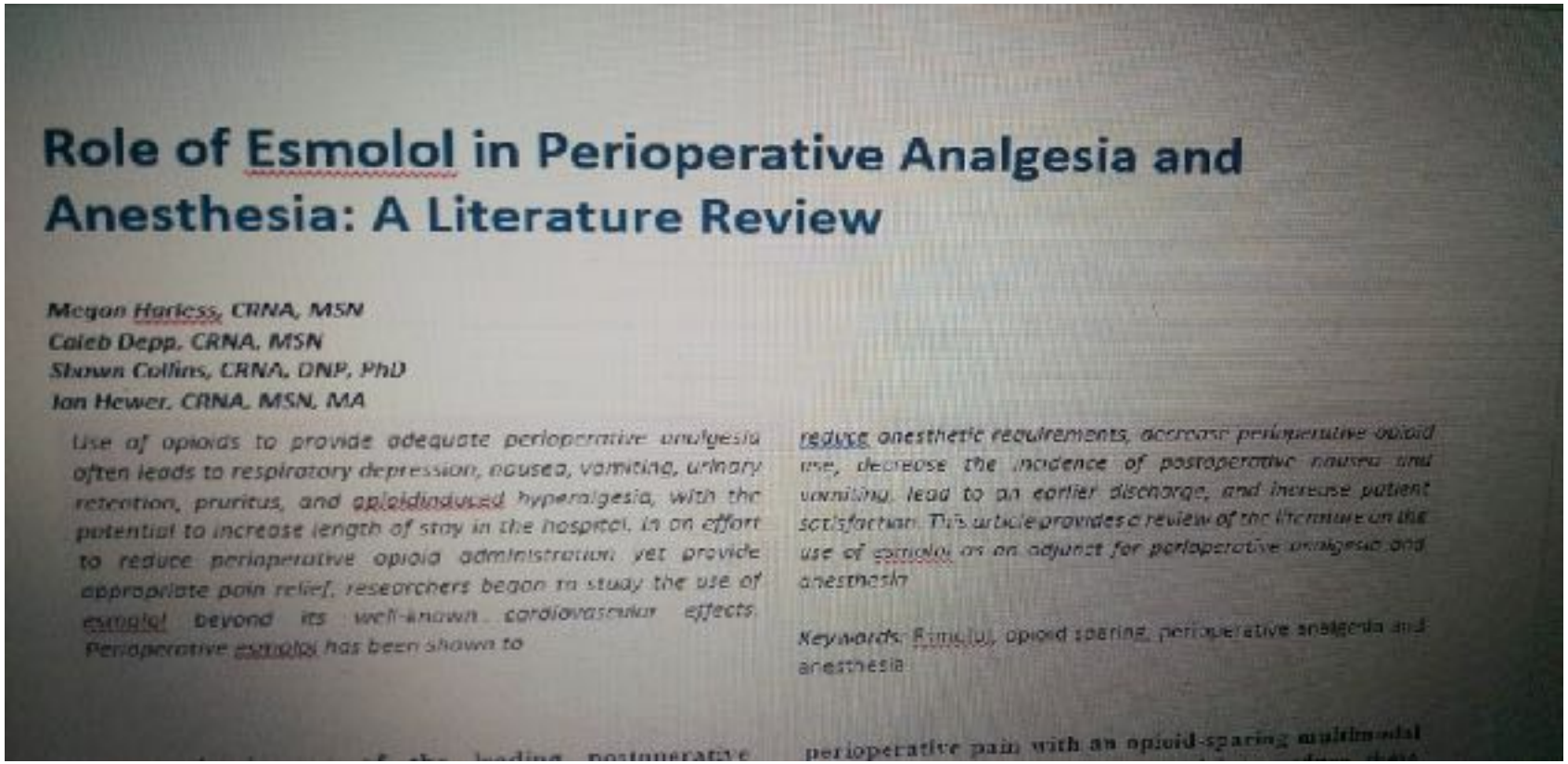
Case: 41 yo G8P3043 woman presented at 39 weeks for labor induction. At complete cervical dilation, the patient complained of shortness of breath. Oxygen saturation decreased to 80% and within 1 minute she developed cardiac arrest. ACLS was initiated and the baby was quickly delivered via forceps. The 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 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:

1. Armstrong DJ, Miller SA. The role of platelets in the reflex tachypnoeic response to miliary pulmonary embolism in anaesthetized rabbits. Exp Physiol 1990;75:791-800.
2. Leanos OL, et al. Reflex circulatory collapse following intrapulmonary entrapment of activated platelets: Mediation via 5-HT3 receptor stimulation. Br J Pharmacol 1995;116:2048-52.
3. James CF, et al. Massive amniotic fluid embolism: Diagnosis aided by emergency transesophageal echocardiography. Int J Obstet Anesth 2004;13:279-83.

AANA Journal June 2015



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

Megan Harless, CRNA, MSN
Caleb Depp, CRNA, MSN
Shawn Collins, CRNA, DNP, PhD
Ian 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

perioperative pain with an opioid-sparing multimodal

Can you do a anesthetic without narcotics?

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Not Everything is it appears?
Labor Epidurals going away?

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

Is Nitrous Back? 2009

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.

Lowe, NK. The nature of labor pain. Am J Obstet Gynecology 2002;186(5):S16–24.
Marmor TR,Krol DM. Labor pain management in the United States: Understanding patterns and the issue of choice. Am J Obstet Gynecology 2002;186:S173–80.
Rooks JP. Nitrous oxide for pain in labor – why not in the United States? Birth 2007;34:3–.
Rosen MA. Nitrous oxide for relief of labor pain: A systematic review. Am J Obstet Gynecology 2002;186:S110–26
Declercq ER, Sakala C, Corry MP, Applebaum S. Listening to Mothers LL: Report f the Second National U.S. Survey of Women's Childbearing Experiences. New York: Childbirth Connection, October 2006, p. 31.

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

Share this content:

Despite lower reported effectiveness for 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*.[1]

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.[2,3] 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.

2002; 186(5 Suppl Nature): S110-28.

3. Likis FE, Andrews JC, Collins MR, et al. Nitrous oxide for the management of labor pain: a systematic review. ***Anesth Analg***. 2014; 118(1):153-67. doi: 10.1213/ANE.0b013e3182a7f73c

4. Hodnett ED. Pain and women's satisfaction with the experience of childbirth: a systematic review. ***Am J Obstet Gynecol***. 2002; 186(5 Suppl Nature): S160-72.

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Tranexamic Acid

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

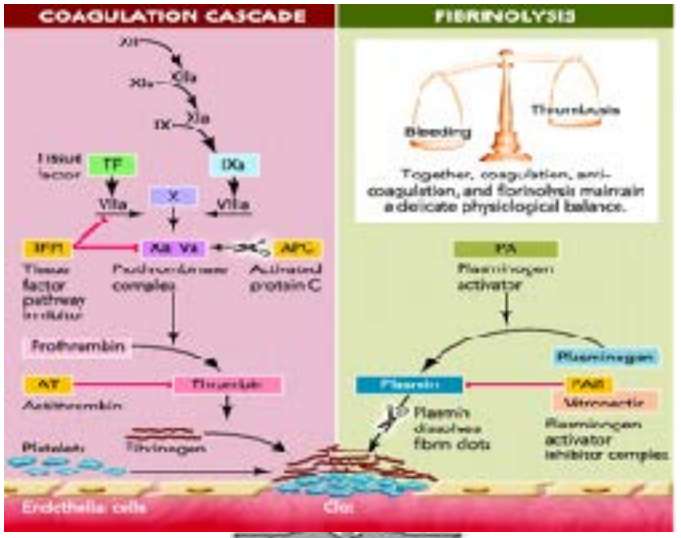
Give within 3 hours- 1gm in 100mL NS over 10 mins

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

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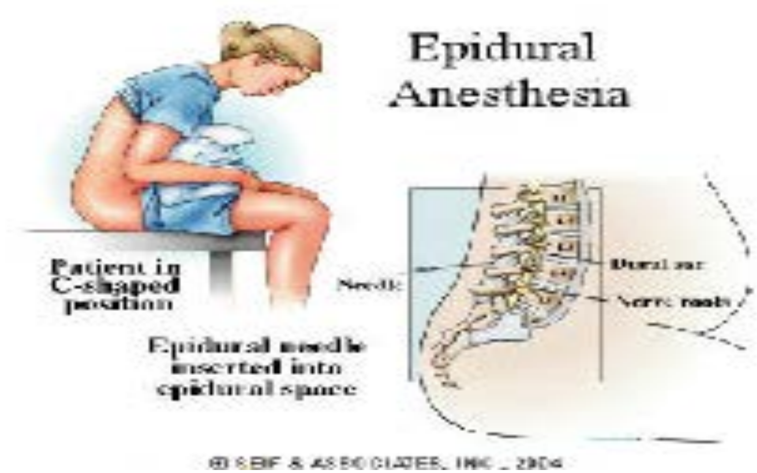
Anesth Analg. 2005 Nov;101(5):1516-20.
Prophylactic intravenous ondansetron and dolasetron in intrathecal morphine-induced pruritus: a randomized, double-blinded, placebo-controlled study.

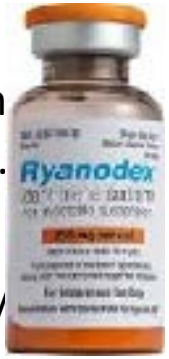
Anesthesiology, 2015; 15(18)



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.

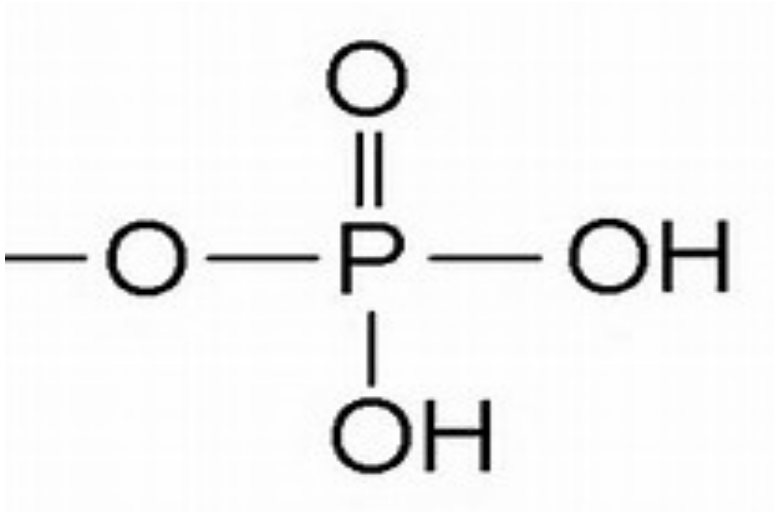
NOT FOR GENERAL

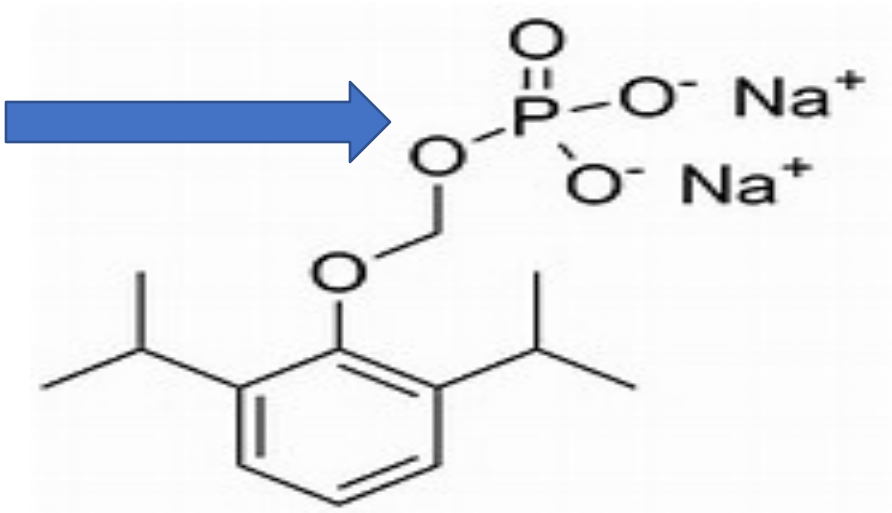
This will and has already raised some concern—FDA states that only those trained in delivering anesthesia should use

this drug. What about the ago old question??

What about using this in GI clinic

Fospropofol (Lusedra)





Trollway Anesthesia: 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 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 ($MgSO_4$) 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 $MgSO_4$ plus lidocaine on suppressing propofol injection pain.

Methods: Three hundred women received 300 mg $MgSO_4$ (Group M), 40 mg lidocaine (Group L), or 300 mg $MgSO_4$ 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.[1] 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.[1–7] 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.[8] A meta analysis[1] suggested that use of a rubber tourniquet and lidocaine application before propofol injection was most effective to prevent injection pain. Dae et al[9] 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

BRIEF REPORT

The Use of Magnesium Sulfate to Prevent Pain on Injection of Propofol

Dilek Memiş*, Alparslan Turan*, Beyhan Karamanlıoğlu*, Necdet Süt†, and Zafer Pamukçu*

Departments of *Anesthesiology and †Biostatistics, Trakya University Medical Faculty, Edirne, Turkey

Magnesium sulfate with lidocaine for preventing propofol injection pain: a randomized, double-blind, placebo-controlled trial

Authors

Authors and affiliations

Citations

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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*

Trollway Anesthesia

Life Lo

Remimazolam

Competitive Product Profile for Remimazolam

General anaesthesia

Product Profiles	Remimazolam	Propofol	Sevoflurane
Rapid time to peak effect	✓	✓	✓
Rapid offset	✓	✓	✓
Predictable recovery time	✓	✓	✓
Early discharge	✓	✓	✓
Low respiratory depression	✓	✗	✗
Cardiostability	✓	✗	✗
Early recovery to full cognition	✓	✗	✗
Reversal agent available	✓	✗	✗
Low re-sedation risk after reversal	✓	-	-
No (low) pain on injection	✓	✗	-
Low risk of excitation[1]	✓	✓	✗
No risk of theatre contamination	✓	✓	✗
No risk of atmospheric pollution	✓	✓	✗
Simple equipment to handle	✓	✓	✗

[1]during induction of narcosis

- Analogue of Midazolam
  - ► that utilizes the ester design.
  - ► Broken down by nonspecific ester hydrolysis
- Designed for out patient 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

- **<u>6mg loading Dose followed by 3 mg maintenance doses</u>**

- Crazy but initial studies have not change in ventilation or oxygenation with remidmazolam with NO supplemental oxygen applied…….

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

« 3 Pharmaceutical Stocks t How mi lealth Will Change t »

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

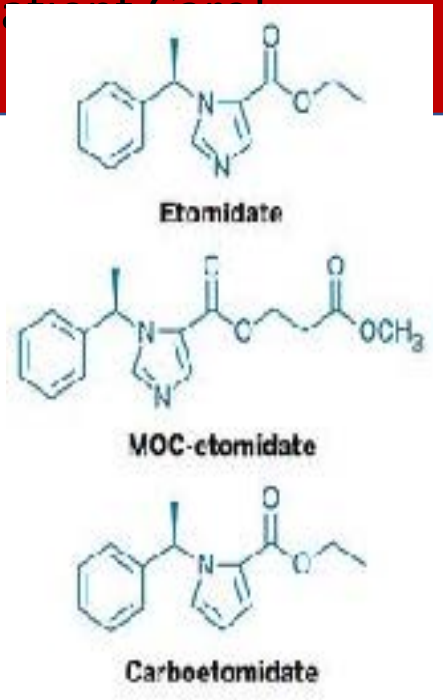
^ Rogers WK, McDowell TS (December 2010). "Remimazolam, a short-acting GABA(A) receptor agonist for intravenous sedation and/or anesthesia in day case surgical and non surgical procedures". *IDrugs : the investigational Drugs Journal* 13 (12): 929–37. PMID 21154153

Etomidate --MOC

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



Curr Pharm. Des.
2012;18(38):6253-6.
Novel etomidate dérivatives.
Sneyd JR[1].

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Carboetomidate

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

- ??? Benefit ???

Phaxan

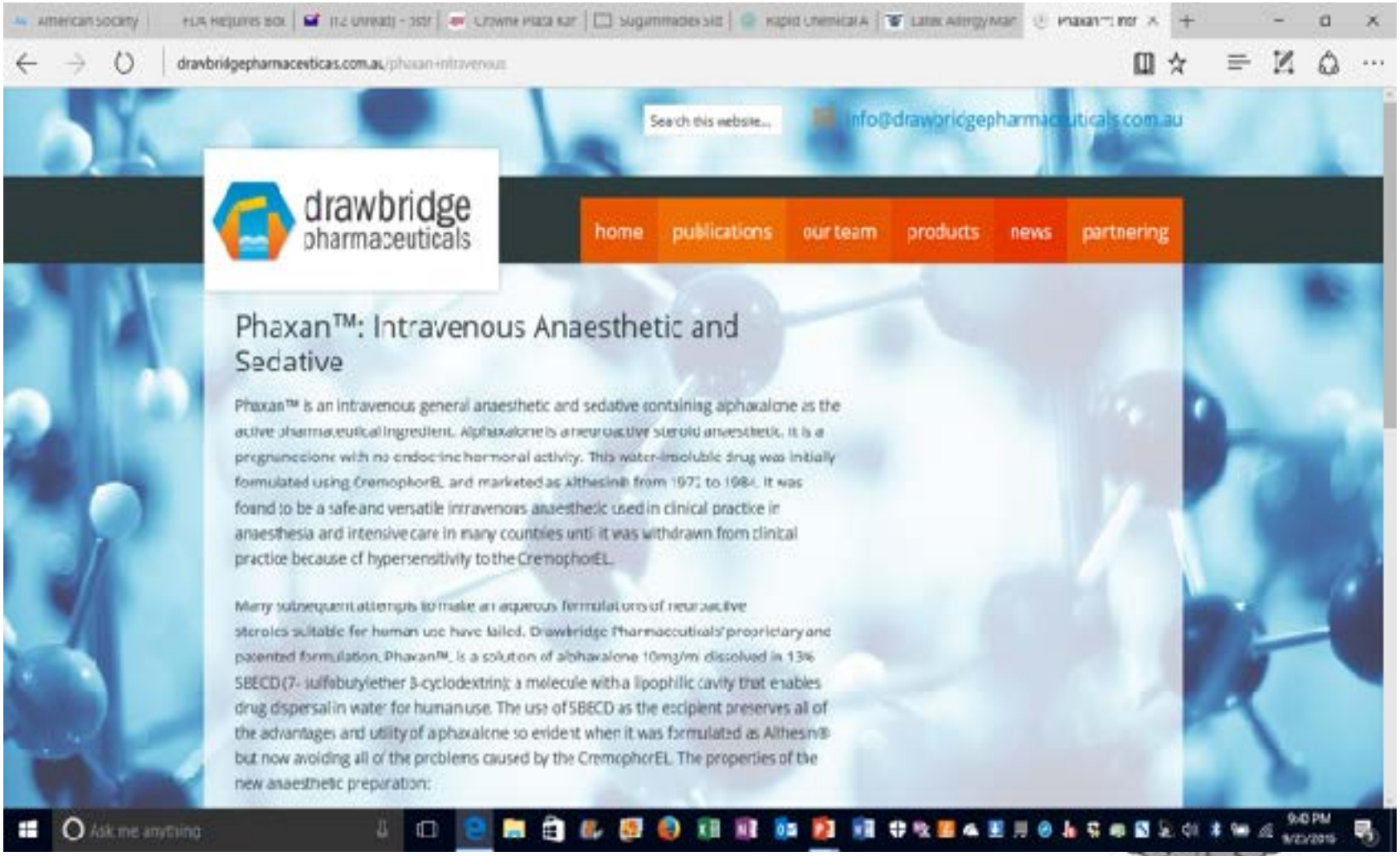
Water-based clear, colorless solution that is easy to manufacture.

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??



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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.
- **<u>What if we could add it to our Blocks? Increase our Duration!</u>**

Trollway Anesthesia

Anesthesiology 2011;115:575-88

De Oliveira GS Jr, Almeida MD, Benzon HT, McCarthy RJ

- 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.

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British Journal of Anaesthesia **107** (3): 446–53 (2011)
Advance Access publication 14 June 2011 · doi:10.1093/bja/aer159

BJA

Effect of dexamethasone on the duration of interscalene nerve blocks with ropivacaine or bupivacaine

K. C. Cummings III[1,2*], D. E. Napierkowski[4], I. Parra-Sanchez[2], A. Kurz[2], J. E. Dalton[2,3], J. J. Brems[5] and D. I. Sessler[2]

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* Corresponding author: 9500 Euclid Ave, Mailcode E30, Cleveland, OH 44195, USA. E-mail: cummink2@ccf.org

Editor's key points

- This trial demonstrates a difference in block

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

Original article 285

Dexamethasone with bupivacaine increases duration of analgesia in ultrasound-guided interscalene brachial plexus blockade

Peter A. Vieira, Istvan Pulai, George C. Tsao, Poomachandran Manikantan, Brunella Keller and Neil Roy Connelly

Background and objectives Dexamethasone has been shown to prolong the duration of postoperative analgesia when given as an adjunct to peripheral nerve blocks. However, it has not been evaluated when given in conjunction with bupivacaine and clonidine to provide blockade of the brachial plexus at the interscalene level. The purpose of this investigation was to determine whether the addition of dexamethasone to 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 60 individuals undergoing shoulder arthroscopy. Patients received interscalene brachial plexus block using 20 ml of bupivacaine 5 mg ml^{-1} with 1 : 200 000 epinephrine and clonidine 75 μg. Patients were randomly assigned to receive either dexamethasone 8 mg or 0.9% NaCl as an adjuvant to the mixture. After discharge, patients recorded pain scores and analgesic consumption in a diary and estimated 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 demographics, block pain intensity measurements, postoperative analgesic consumption, duration of analgesia and patient satisfaction.

Results Dexamethasone prolonged median sensory (1457 vs. 883 min, $P < 0.0001$) and motor (1374 vs. 827 min, $P < 0.0001$) blockade compared with the control. At 24 h, the dexamethasone group had lower median verbal analogue scale scores compared with control (3.0 vs. 6.0). At 48 h, the two groups had similar median pain scores (4.0 vs. 5.0, dexamethasone vs. control, respectively). The opioid requirement in oxycodone equivalency 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 The addition of dexamethasone to a bupivacaine–epinephrine–clonidine interscalene block prolongs sensory block and reduces opioid use.

Eur J Anaesthesiol 2010;27:285–288

Keywords: ambulatory, anaesthesia, analgesia, brachial plexus, clonidine, orthopaedic, regional

Received 7 June 2009 Revised 2 November 2009
Accepted 5 November 2009

Introduction

Regional anaesthesia has gained much popularity in outpatient orthopaedic surgery. Increasing duration of local anesthetic action by addition of epinephrine prolongs duration of subcutaneous infiltration of local anesthesia.[3]

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.0b013e31828e3901
Ambulatory Anesthesiology: Research Report

Certified Registered Nurse Anesthetist

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
- 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

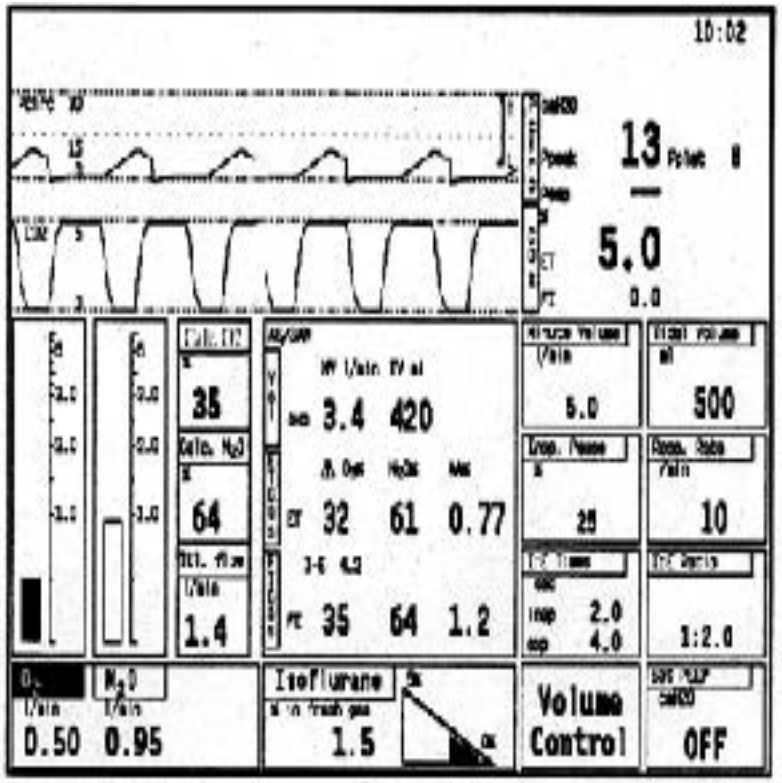
Akynzeo, a combination product of netupitant and palonosetron

Each capsule contains 300 mg of netupitant, and palonosetron hydrochloride equivalent.

Oxygen

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

Perioperative clinical factors & immune function



Supplemental perioperative oxygen improves postop outcomes

FO_2 of 0.8 doubles subcut O_2 tension & halves postop wound infection rate

Supplemental O_2 ↓ PONV after laparoscopies & laparotomies

Curr Opin Anesthesiol 2006;19:11-18

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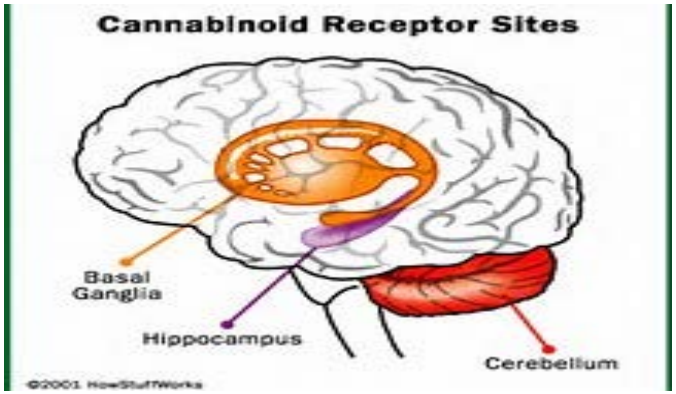
Cannabinoids

Salivex
Ajulemic acid
Nabilone
Marinol
Cannadur
Cannabis



As of 2013; 23 controlled studies looking at Cannabinoids for pain management

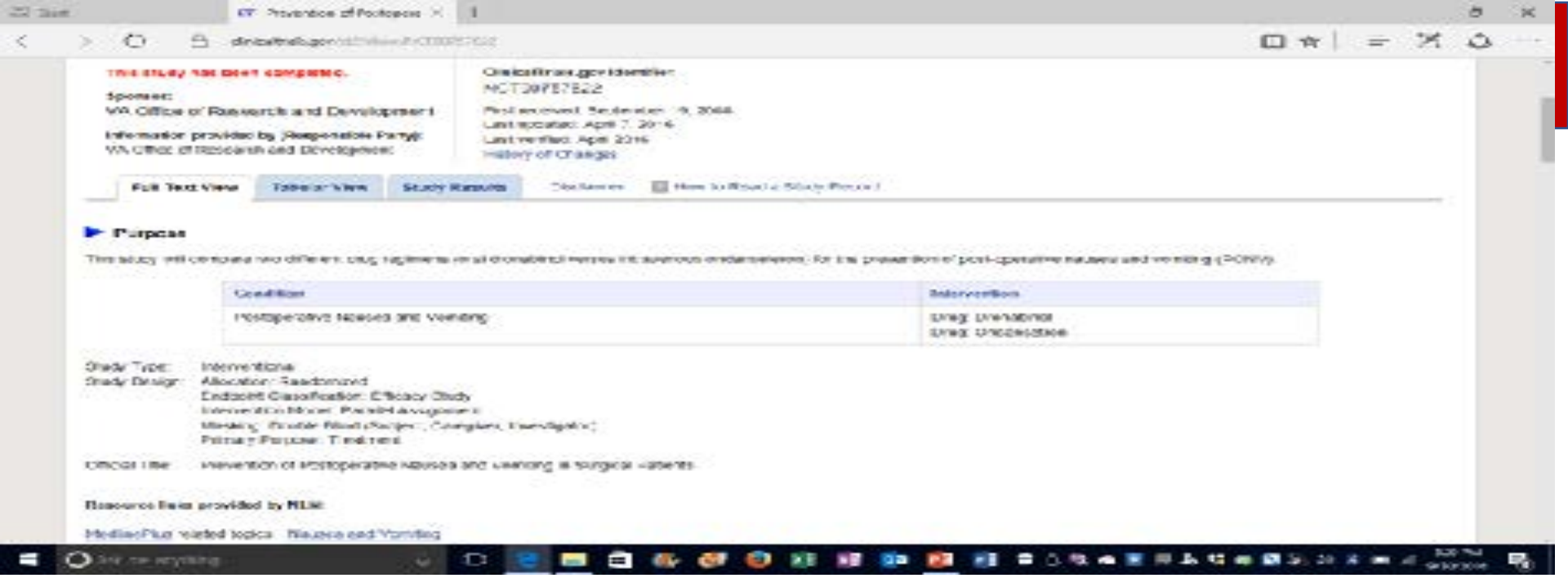
Marinol

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



Sponsor:
VA Office of Research and Development

Information provided by (Responsible Party):
VA Office of Research and Development

ClinicalTrials.gov Identifier:
NCT00787722

First received: September 9, 2008
Last updated: April 7, 2016
Last verified: April 2016
History of Changes

Full Text View | Tabular View | Study Results | Disclaimer | How to Read a Study Record

Purpose

This study will compare two different drug regimens in adult female patients undergoing surgery for the prevention of post-operative nausea and vomiting (PONV).

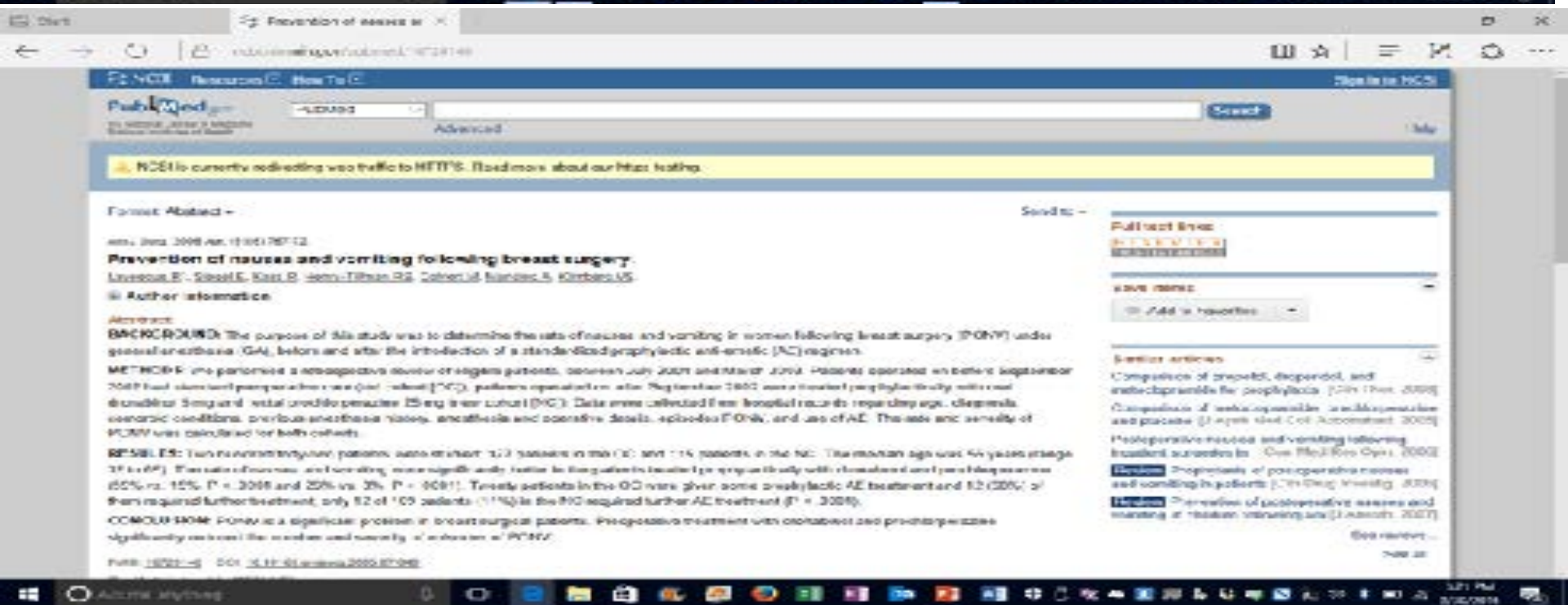
Condition	Intervention
Postoperative Nausea and Vomiting	Drug: Dexamethasone Drug: Ondansetron

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Caregiver, Investigator)
Primary Purpose: Treatment

Official Title: Prevention of Postoperative Nausea and Vomiting in Surgical Patients

Resources links provided by NLM:

MedlinePlus related topics: Nausea and Vomiting



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Format: Abstract

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Prevention of nausea and vomiting following breast surgery.

Author information

Abstract

BACKGROUND: The purpose of this study was to determine the rate of nausea and vomiting in women following breast surgery (PONV) under general anesthesia (GA), before and after the introduction of a standardized prophylactic anti-emetic (AC) regimen.

METHODS: We performed a retrospective review of ... patients. Between July 2001 and March 2004, ... patients operated on before September 2007 had received perioperative ... (control [PC]); patients operated on after September 2007 were treated prophylactically with oral dexamethasone 8 mg and ... (AC). Data were collected from hospital records regarding age, diagnosis, comorbid conditions, previous anesthesia history, anesthesia and operative details, episodes of PONV, and use of AE. The rate and severity of PONV was calculated for both cohorts.

RESULTS: Two hundred ... patients were enrolled: 123 patients in the PC and 116 patients in the AC. The median age was 54 years (range 21 to 87). The rate of nausea and vomiting were significantly better in the patients treated prophylactically with dexamethasone and ... (55% vs. 15%, P < .0001 and 25% vs. 3%, P = .0001). Twenty patients in the PC were given some prophylactic AE treatment and 12 (20%) of them required further treatment; only 12 of 109 patients (11%) in the AC required further AE treatment (P = .0095).

CONCLUSIONS: PONV is a significant problem in breast surgical patients. Perioperative treatment with dexamethasone and ... significantly reduces the incidence and severity of subsequent PONV.

PMID: ... DOI: ...

2013

(11 unread) - pstrube | My eBay Summary | kehlet h, dahl jb. anes | Society Blog View | A | A 'civil war' over pain | gralise - Bing | Russo-Hohmann

theroc.us/images/Russo-Hohmann%20Role%20of%20cannabinoids%20in%20pain%20management%20from%20Deer%202013.pdf

Role of Cannabinoids in Pain Management

18

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 prototypic 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 Δ^9-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 endovanilloid 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

Type or talk to search

11:21 AM 2/17/2017

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……

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**. 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

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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; opicid: 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 554 patients. ZOFRAN 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 8. Prevention of Postoperative Nausea and Vomiting in Adult Patients

	Ondansetron 4 mg I.V.	Placebo	*P* Value
Study 1			
Emetic episodes: Number of patients Treatment response over 24-h postoperative period	136	139	
0 Emetic episodes	103 (76%)	64 (46%)	<0.001
1 Emetic episode	13 (10%)	17 (12%)	
More than 1 emetic episode/rescued	20 (15%)	58 (42%)	
Nausea assessments: Number of patients No nausea over 24-h postoperative period	134 56 (42%)	136 39 (29%)	
Study 2			
Emetic episodes:			

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.

Clinical Research Article

Korean J Anesthesiol 2012 April 62(4) 343-349
http://dx.doi.org/10.4097/kjae.2012.62.4.343

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

Dae Seong Kim, Gil Hoi Koo, Hyun Kang, Chong Wha Baek, Yong Hun Jung, Young Cheol Woo, Jin Yun Kim, and Sun Gyun 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

Lee Y, Wang JJ, Yang YL, Chen A, Lai HY. Midazolam vs ondansetron for preventing postoperative nausea and vomiting: a randomized controlled trial. Anaesthesia. 2007;62(1):18-22.

Trollway Anesthesia

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#

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Blood Pressure

The BEST treatment of choice for beta-blocker overdose is?

A. Glucagon
B. Methylene Blue
C. Esmolol
D. Vasopressin

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

Glucagon must be reconstituted immediately prior to administration.

http://store.mcguff.com/products/3388.aspx

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

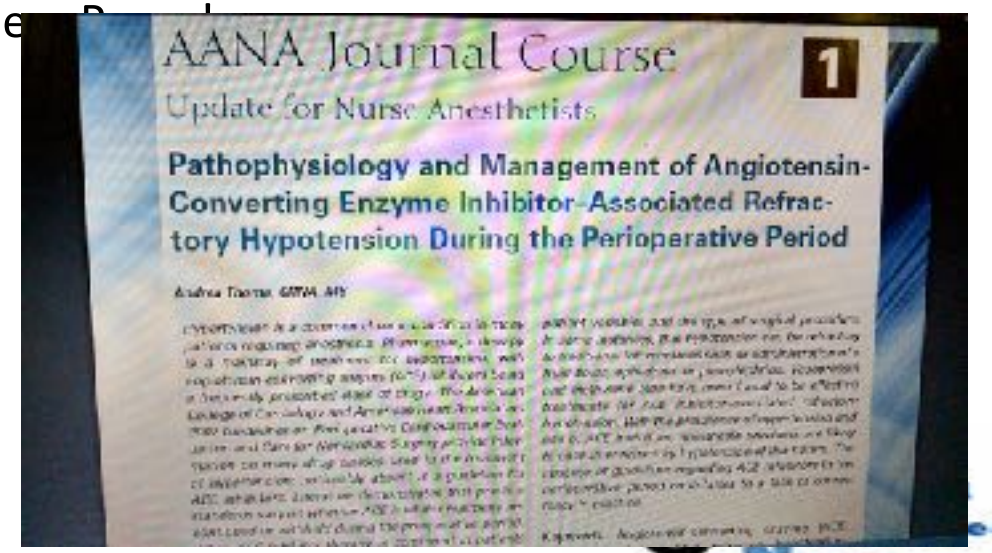
Hypotensive Thought Pattern

- 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 Weinbe
- 5 vasopressin

- What is 6 for you?

- ?? Glucagon


AANA Journal Course 1
Update for Nurse Anesthetists

Pathophysiology and Management of Angiotensin-Converting Enzyme Inhibitor–Associated Refractory Hypotension During the Perioperative Period

Nurse Anesthetist

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

http://dailyem.wordpress.com/category/hydrocortisone/

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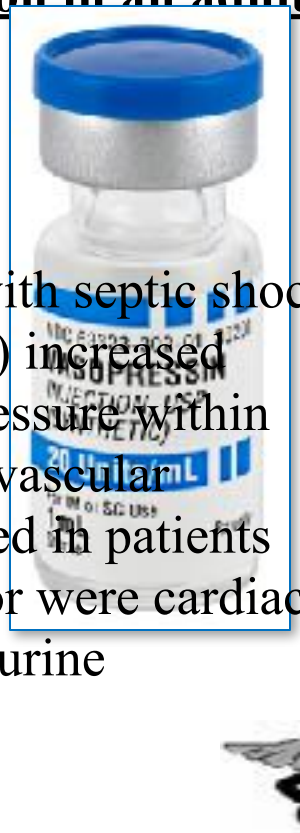
Dosing of Vasopressin

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

Reason for the Shortage American Regent discontinued vasopressin injection in early 2015.1,2 Par Sterile Products (formerly JHP) discontinued Pitressin injection in November 2014

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.

See more at: http://www.ashp.org/menu/DrugShortages/CurrentShortages/bulletin.aspx?id=795#sthash.XkiyeTLH.dpuf

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

See more at: http://www.ashp.org/menu/DrugShortages/CurrentShortages/bulletin.aspx?id=795#sthash.XkiyeTLH.dpuf

New Pain Drugs

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

- Antidote: Entereg
  - (almivopam)

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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 curtailing opioid prescribing. The other group looks at the disability, the human suffering, the expense of chronic pain."

September 26, 2016

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.

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Multimodal Approach to Acute Pain Management

Severe Pain

Moderate Pain

Mild Pain

STEP 3
STEP 2
and
Higher doses of opioids

STEP 2
STEP 1
and
Low doses of opioids

STEP 1
Acetaminophen, NSAIDs, or COXIBs
and
Local/regional anesthesia

Modified from Crews et al., 2002[1]

1. Crews JC. *JAMA*. 2002;288:629-632. 2. World Health Organization. Pain relief ladder. http://www.who.int. Accessed November 21, 2011. 3. Ventafridda V, et al. *Cancer*. 1987;59:850-856. 4. ASA Task Force. *Anesthesiology*. 2004;100:1573-1581.

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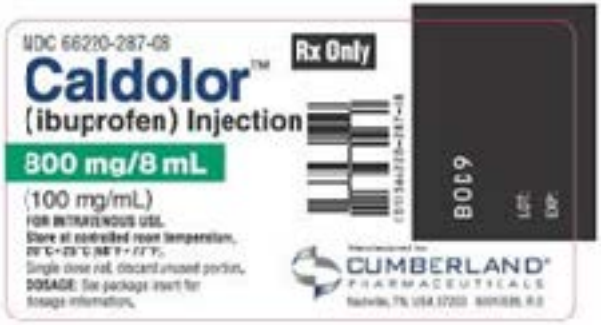
We Must Start to Think Differently!

Multi-Modal

Synergy

Pre-emptive

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



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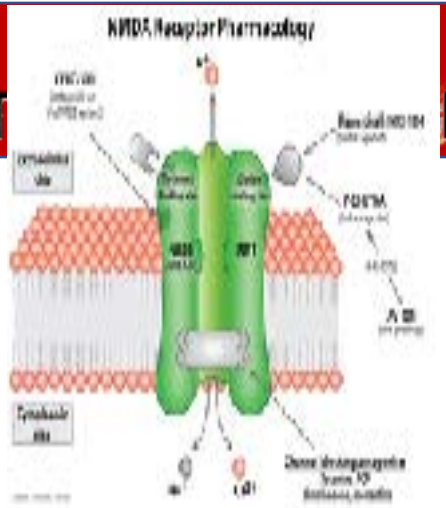

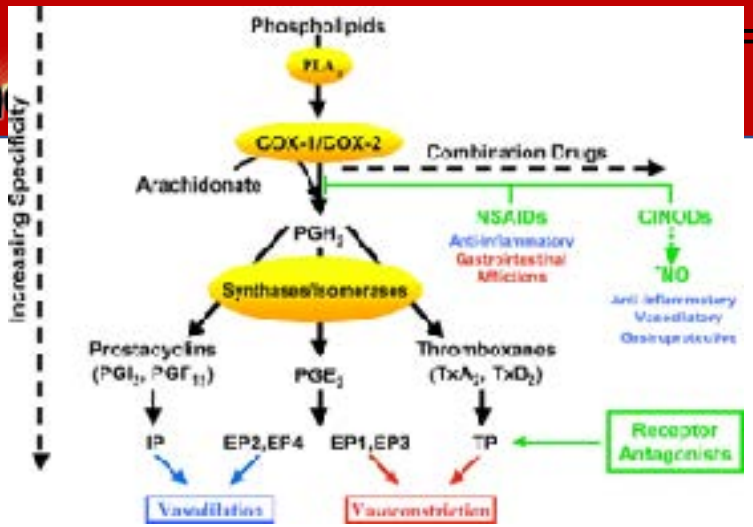

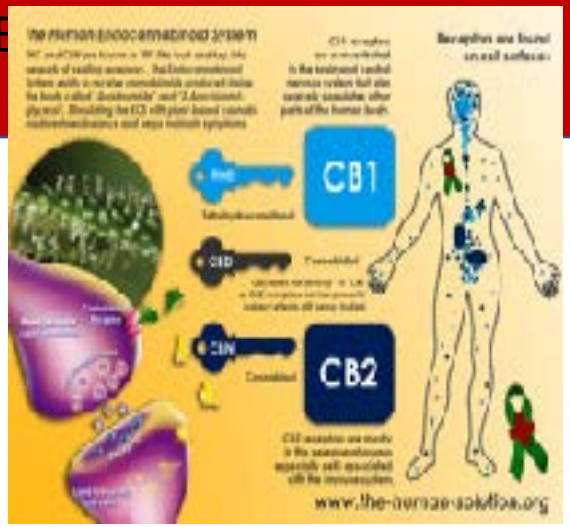

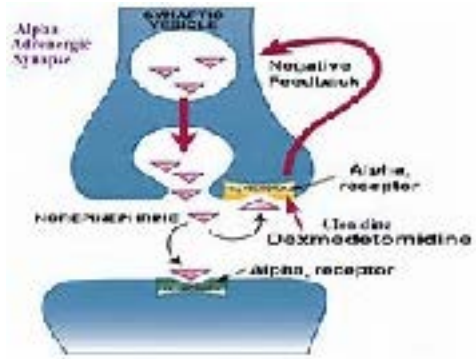

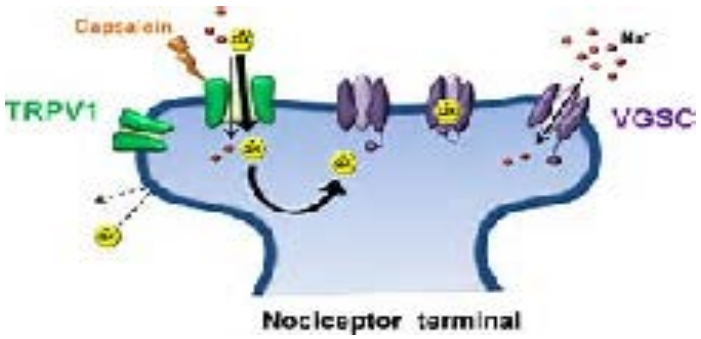

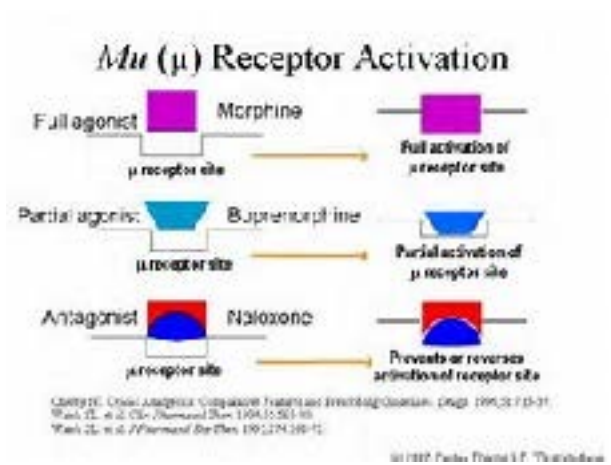

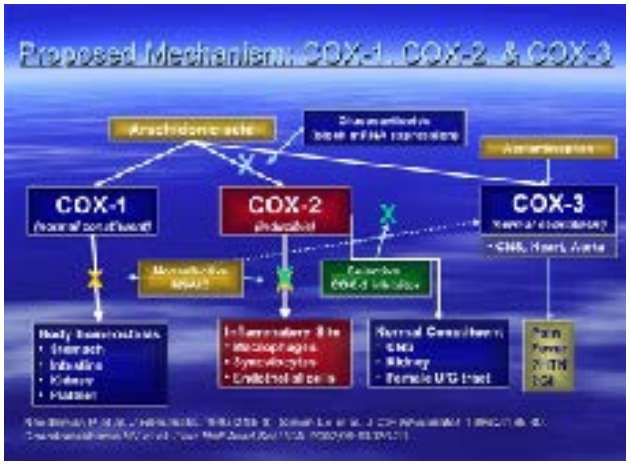

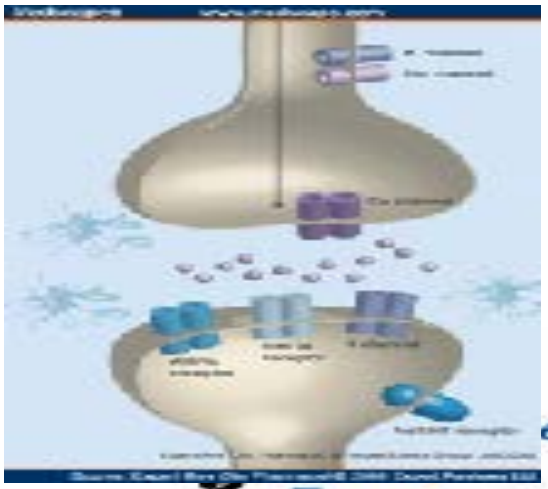

OFIRMEV $10.00/1000mg

- 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.

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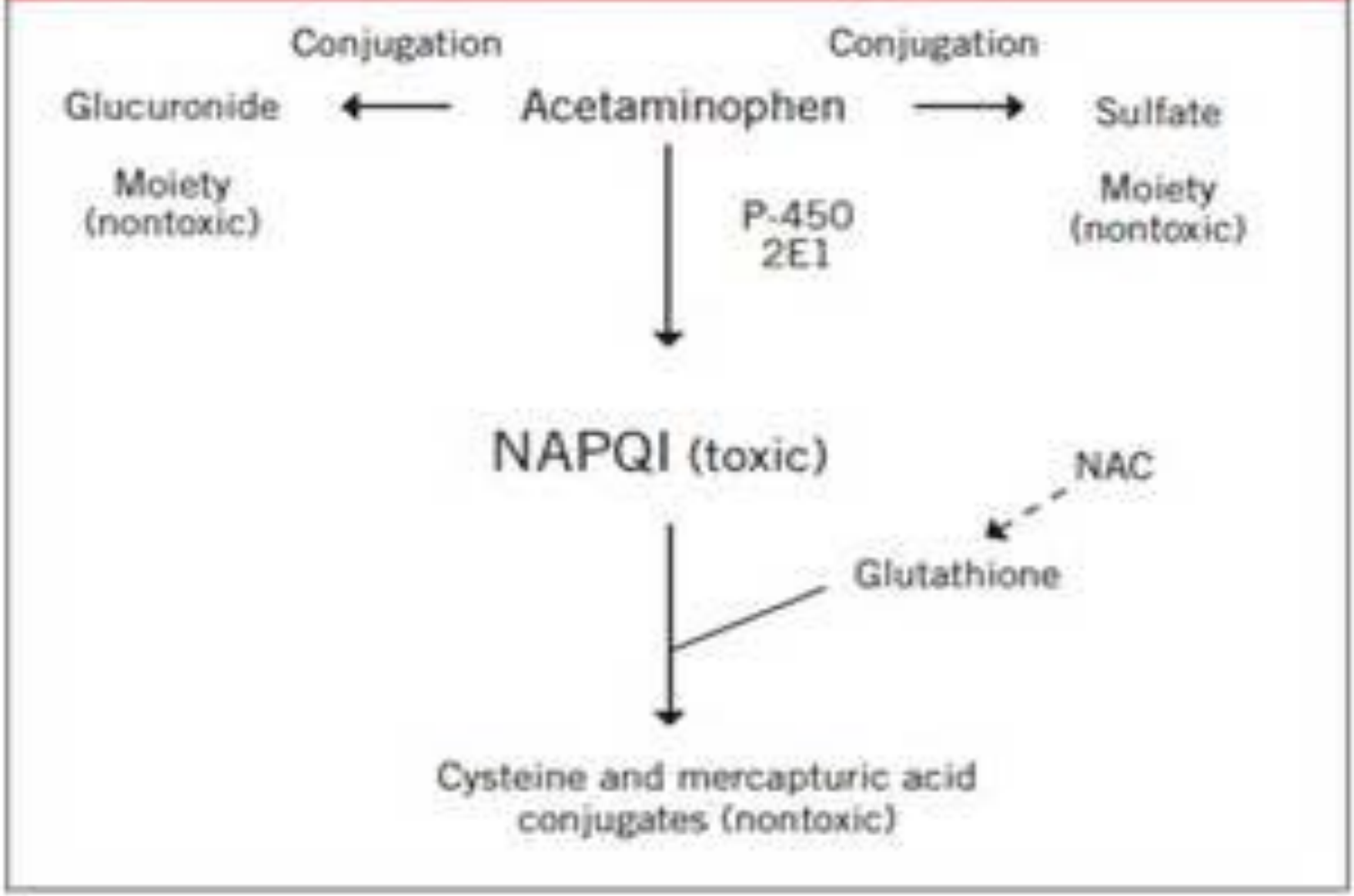
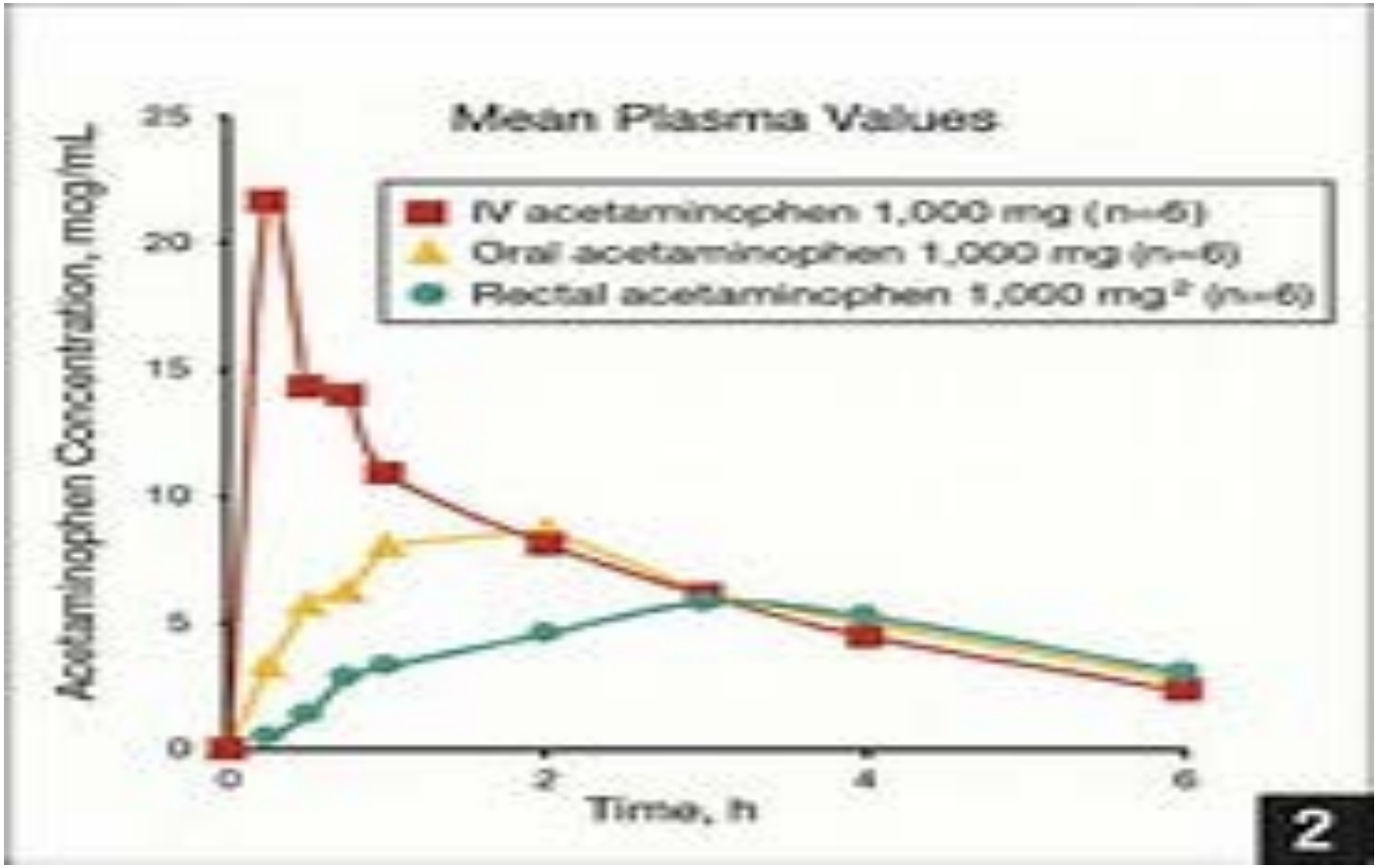
Figure 1 – Acetaminophen metabolism




Mean Plasma Values
IV acetaminophen 1,000 mg (n=6)
Oral acetaminophen 1,000 mg (n=6)
Rectal acetaminophen 1,000 mg[2] (n=6)
Acetaminophen Concentration, mcg/mL
25
20
15
10
5
0
0
2
4
6
Time, h
2

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.[1] Two COX isozymes, COX-1 and -2, were first identified in the early 1990's as the catalysts for an important step in prostaglandin biosynthesis.[2] Although both enzymes have similar functions, their temporal and spatial expression patterns are very different.[3] 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 gastroprotection.[4] In contrast, COX-2 expression is primarily induced by factors such as endotoxins, cytokines, and growth factors.[5] COX-2 is expressed at sites of inflammation and produces prostaglandins that mediate inflammatory and pain sensation responses.[6] COX 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.[7-9]

Finally, identification of a new isozyme, COX-3, suggests that it is the target for acetaminophen.[9] 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 2.6 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 these 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.[9]

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

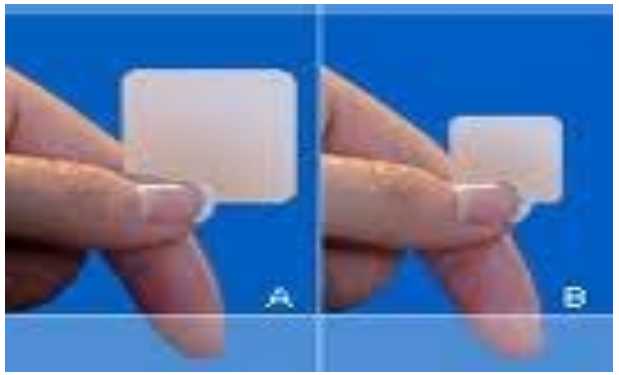
- Think about Ketorolac.. Actions and side effects
- Big differences… Less action on Cox 1 and more Cox 2 action..
- What does this mean? Less bleeding.. More pain control can give anytime during the surgery… better now that we can give per--op
- 400mg/4ml or 800mg/8ml
- Dilute and administer over 30 minutes
- 400mg-800mg Over 30 min repeat every 6 hours PRN*
- Fluids " well hydrated prior to use"

Alkermes Pharm—Meloxicam IV

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.

Lots of exciting information coming about related to Meloxicam! More COX 2 than previous thought

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….**

Certified Registered Nurse Anesthetist

Sufentanil 30 mg tablet

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.

2017, Neil Singla, Harold Minkowitz, Tong-Joo Gan,Yu-kun Chiang, Karen DiDonato, Pamela Palmer

DSUVIA-Sublinqual 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

Transmucosal Fentanyl

INSYS THERAPEUTICS, INC.

SUBSYS®

(fentanyl sublingual spray)

100,200,400,600,800,1200,1600 mcg

www.subsysspray.com.

Actiq®

(fentanyl citrate) oral transmucosal lozenge

Figure 2.

Precedex

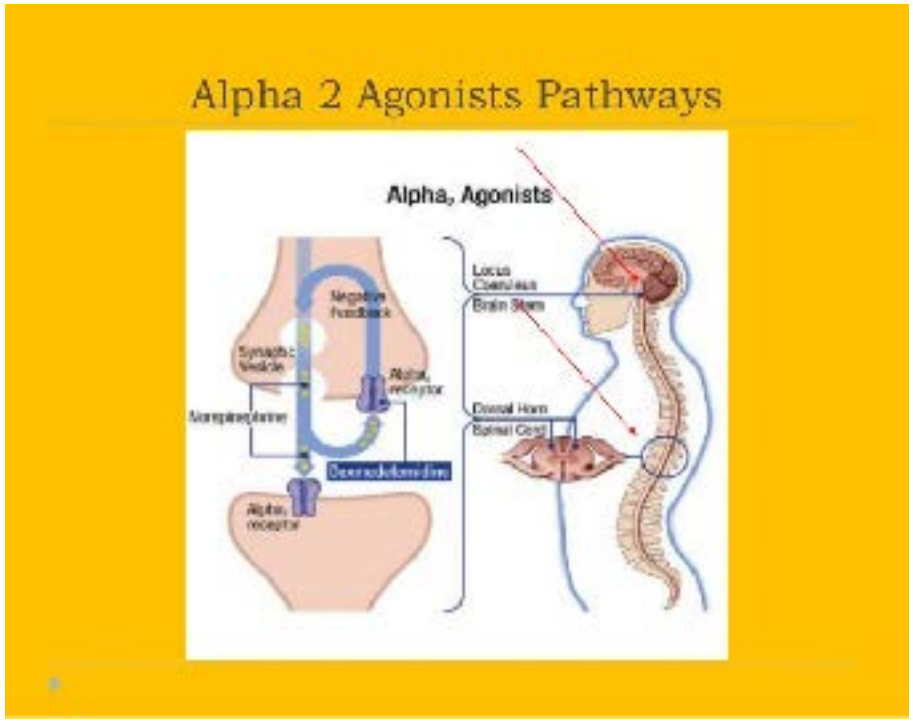
Precedex® (dexmedetomidine HCl Injection)

Zhonghua Yi Xue Za Zhi. 2017 Jan 24;97(4):295-299. doi: 10.3760/cma.j.issn.0376-2491.2017.04.012.

[Effect of dexmedetomidine alone for postoperative analgesia after laparoscopic cholecystectomy].

[Article in Chinese; Abstract available in Chinese from the publisher]

Chen XH[1], Wang ZJ, Xiang QM, Zheng JW.



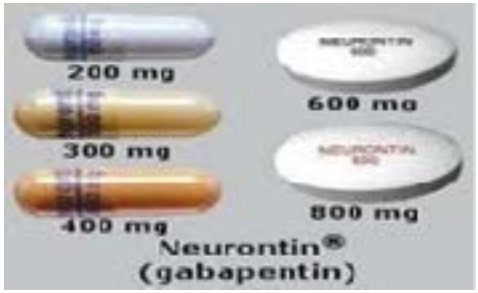
Recro Pharm Dex-IN

Recro's Dex-IN, an intraranasal 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

- Gabapentin is typically well tolerated in the correct does:
- Doses range 300-1200 mg single does for anesthesia : max dose is 1200mg TID or max of 3600mg/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 does (300-600) little problems
- Keep in mind Half life of 5-7 hrs

J Pain Res. 2016 Sep 12;9:631-40. doi: 10.2147/JPR.S112025. eCollection 2016.

Use of preoperative gabapentin significantly reduces postoperative opioid consumption: a meta-analysis.

Arumugam S[1], Lau CS[2], Chamberlain RS[3].

Author information

Abstract

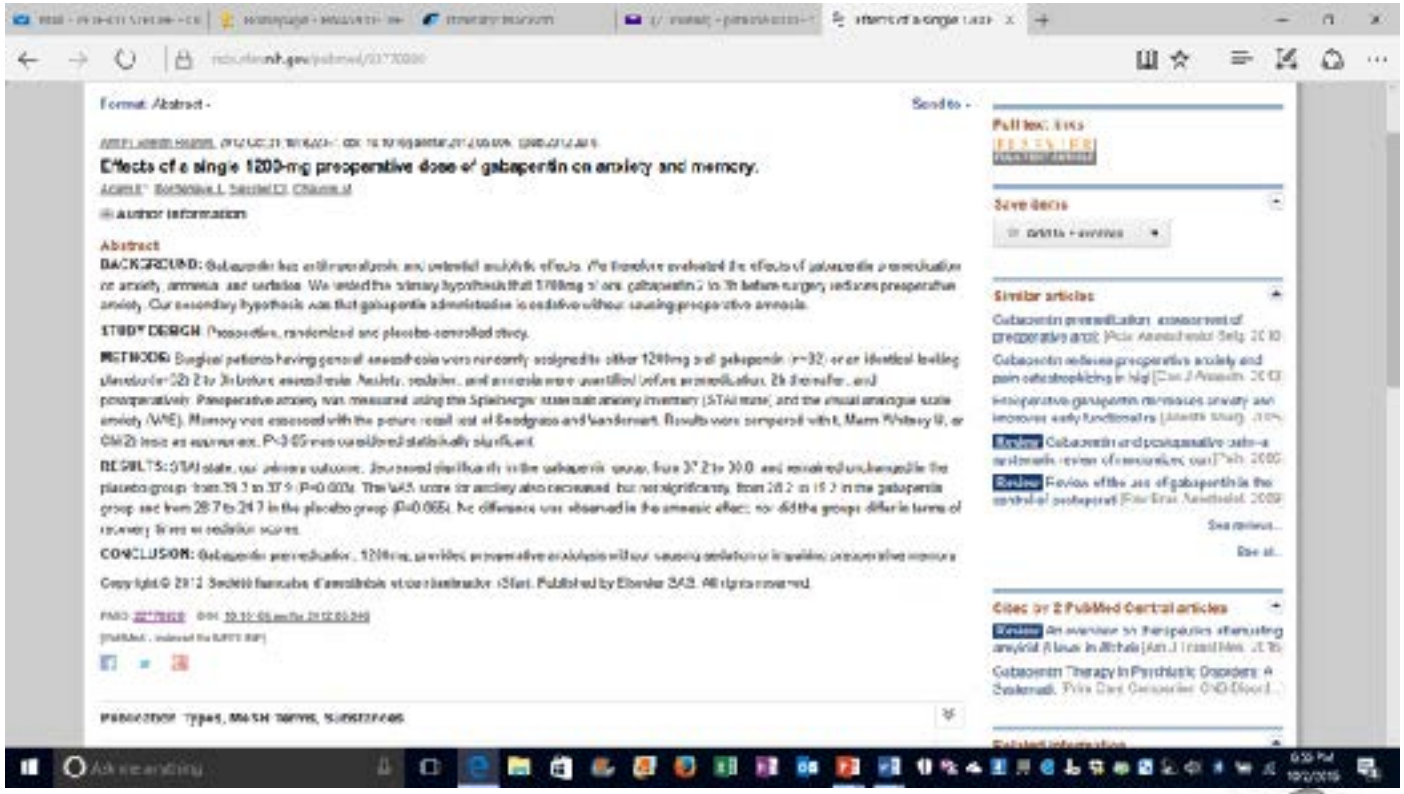
OBJECTIVES: Effective postoperative pain management is crucial in the care of surgical patients. Opioids, which are commonly used in managing postoperative pain, have a potential for tolerance and addiction, along with sedating side effects. Gabapentin's use as a multimodal analgesic regimen to treat 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 control trials that evaluated preoperative gabapentin on postoperative opioid consumption. The outcomes of interest were cumulative opioid consumption following the surgery and the incidence of vomiting, somnolence, and nausea.

RESULTS: A total of 1,793 patients involved in 17 randomized control trials formed the final analysis for this study. Postoperative opioid consumption was reduced when using gabapentin within the initial 24 hours following surgery (standard mean difference -1.35, 95% confidence interval [CI], -1.96 to -0.73, P<0.001). There was a significant reduction in morphine, fentanyl, and tramadol consumption (P<0.05). While a significant increase in postoperative somnolence incidence was observed (relative risk 1.91, 95% CI 1.10-3.31, P=0.02), there were no significant effects 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 incidences. The results from this study demonstrate that gabapentin is more beneficial in mastectomy and spinal, abdominal, and thyroid surgeries. Gabapentin is an effective analgesic adjunct, and clinicians should consider its use in multimodal treatment plans among patients undergoing elective surgery.

Gabapentin not just for pain!



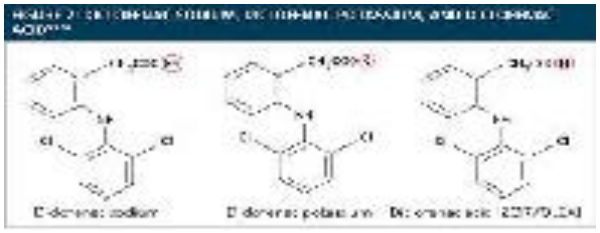
Certified Registered Nurse Anesthetist

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.



Dyloject (Diclofenac)

LAKE FOREST, Ill., Dec. 30, 2014 /PRNewswire/ -- 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.

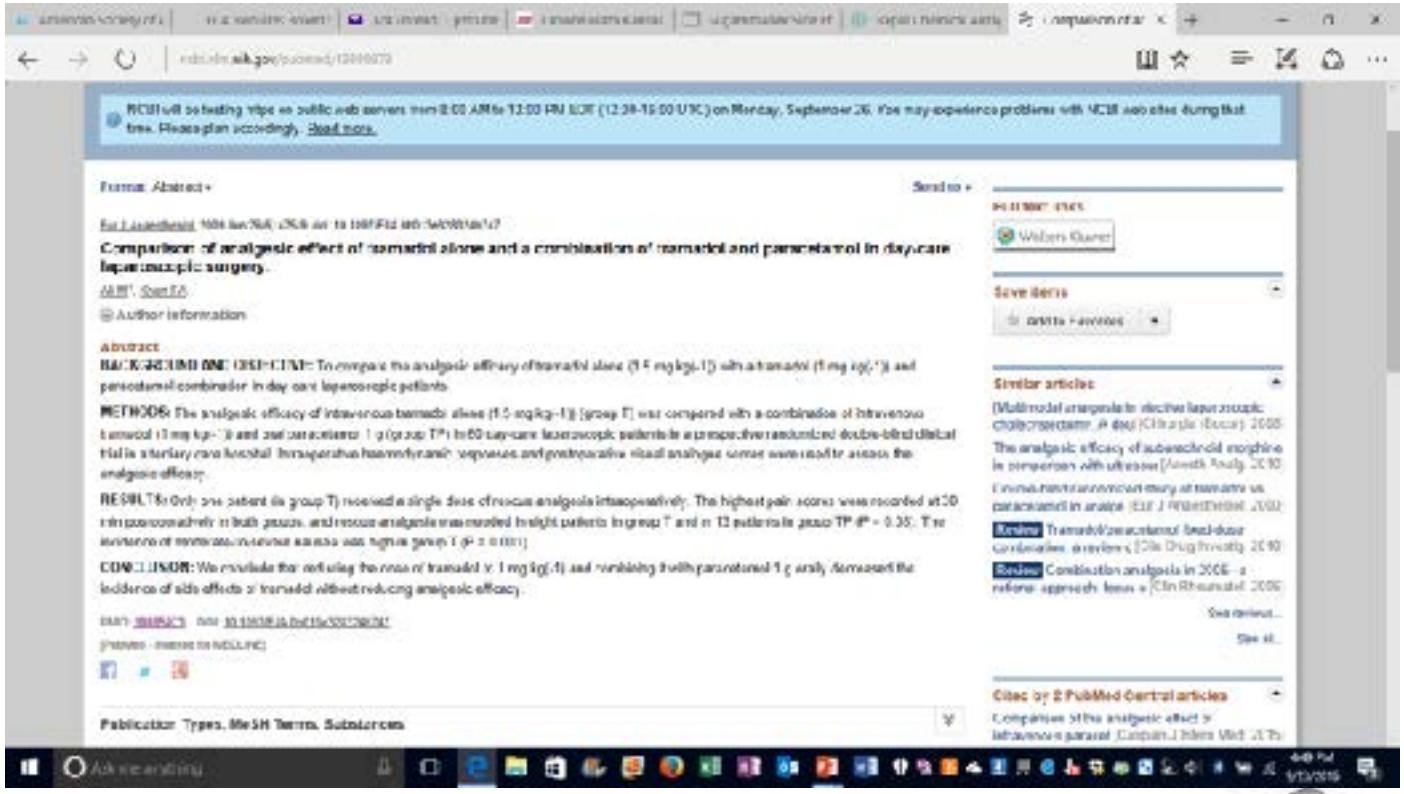
"While not a replacement for opioids, Dyloject is [an] injectable therapy option that can be administered more conveniently in a small-volume, intravenous bolus over 15 seconds as opposed to other injectable non-opioid analgesics that are formulated in large volumes or require dilution prior to administration and typically require an infusion of 15 to 30 minutes to administer the full dose,"

DYLOJECT

ertified
egistered
urse
Anesthetist

Tramadol (1-3 mg/kg)

Single Pre-Operative Dose



IV Tramadol

Tramadol Infusion for Postthoracotomy Pain Relief: A Placebo-Controlled Comparison with Epidural Morphine

Bloch, Mark D. FCA (SA)*; Dyer, Robert A. FCA (SA)*; Uelijke, Gylvia A. FCA (SA)*; James, Michael F. PhD*†

Anesthesia & Analgesia
March 2002 - Volume 94 - Issue 3 - pp 523-526
doi: 10.1097/00000539-200203000-00009
Cardiovascular Anesthesia: Research Report

J Neurosci Rural Pract. 2017 Jan-Mar;8(1):55-59. doi: 10.4103/0976-3147.196535.

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

Rangovan V, Vivekanan L[1], Gunasekaran D[2], Devikala D[2]

Anesth Pain Med. 2016 Jul 26;6(5):e37778. eCollection 2016.

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

Khajavi MR[1], Navardi M[1], Shariat Moharari R[1], Pourfakhr P[1], Khalili N[2], Etezadi F[1], Imani F[1].

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?

The Patch!

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

Exelon®

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.

Antibiotics

Renal Failure

Liver Failure

Temperature, Ph

Dibucaine Number

•FDA approves the first treatment for dementia of Parkinson's disease. FDA News Release. U.S. Food and Drug Administration. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/*2006/ucm108680.htm Accessed October 16, 2013.*

•*Jeffrey S. FDA approves Exelon Patch for severe Alzheimer's. Available at: http://www.medscape.com/viewarticle/807062 Accessed October 16, 2013.*

•*Baruah J, Easby J, Kessell G. Effects of acetyl cholinesterase inhibitor therapy for Alzheimer's disease on neuromuscular block. Br J Anaesth 2008;100:420.*

Nanoparticles:

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

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
EXPAREL® (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 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 Pacira Pharmaceuticals, Inc. (Pacira) 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 make its distribution violative. See 21 U.S.C. 355(a), 352(f); 331(a), (d), 21 CFR 201.5; 201.100; 201.115; 201.128. In addition, the journal ad is false or misleading because it overstates the efficacy of Exparel. The ad is also

AANA Journal
Legal Briefs
Periodicals
News
Advertising & Sponsorship
Media
In Memoriam
National CRNA Week
Current Events
Convention Daily

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.*

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.

Ask me anything

8:03 PM

Exparel

Certified Registered Nurse Anesthetist

Posidur

- New product just like Exparel
- Except Clear…. Could this be trouble?

Lipid Rescue

LipidRescue™

TREATMENT FOR LOCAL ANESTHETIC-INDUCED CARDIAC ARREST

PLEASE KEEP THIS PROTOCOL ATTACHED TO THE INTRALIPID BAG

- **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?

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
- α_2 agonists
- Tricyclic antidepressants
- Substance P antagonists
- Many nerve toxins

  Benadryl

  Droperidol ????

"LIPID RESCUE" FOR TRICYCLIC ANTIDEPRESSANT CARDIOTOXICITY

Michael Stephen Blaber, MBChB,* Jamal Nasir Khan, MRCP,† Judith Anne Brebner, MRCP,‡ and Rachel McColm, MRCP§

*Department of Cardiology, Sandwell & West Birmingham Hospitals NHS Trust, Birmingham, UK, †Department of Cardiology, University Hospital of North Staffordshire, Newcastle, Stoke-on-Trent, UK, ‡Department of Respiratory Medicine, Sandwell & West Birmingham Hospitals NHS Trust, Birmingham, UK, and §Department of Emergency Medicine, Hereford Hospitals NHS Trust, County Hospital, Hereford, UK

Reprint Address: Jamal Nasir Khan, MRCP, Department of Cardiology, City General Hospital, University Hospital of North Staffordshire, Newcastle Road, Stoke-on-Trent ST4 7QP, UK

Med Lett Drugs Ther. 1968 Nov 20;10(24):99-100.

Innovar injection--a combination of droperidol and fentanyl.

[No authors listed]

Certified Registered Nurse Anesthetist

Harvey M, Cave G Case report: successful lipid resuscitation in multi-drug overdose with predominant tricyclic antidepressant toxidrome. Int J Emerg Med. 2012 Feb 2;5(1):8. [Epub ahead of print]

Blaber MS, Khan JN, Brebner JA, McColm R.J "Lipid Rescue" for Tricyclic Antidepressant Cardiotoxicity. Emerg Med. 2012 Jan 11. [Epub ahead of print]

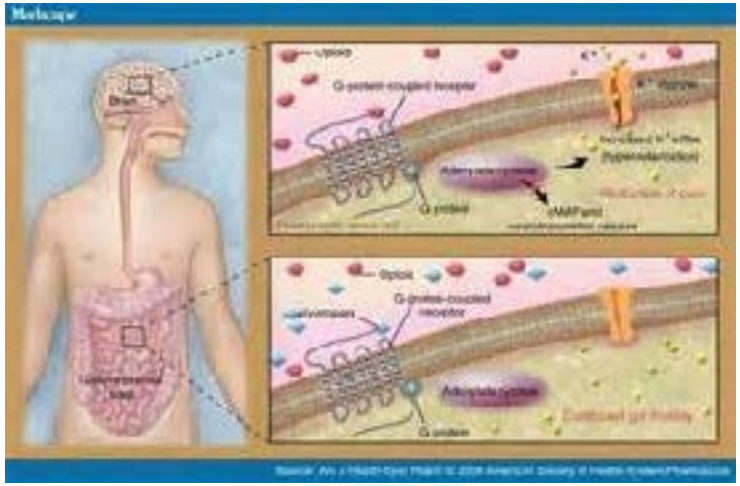
Jakkala-Saibaba R, Morgan PG, Morton GL. Treatment of cocaine overdose with lipid mulsion. Anaesthesia. 2011 Dec;66(12): 1168-70. doi: 10.1111/j.1365-2044.2011.06895.x.

Liang CW, Diamond SJ, Hagg DS. Lipid rescue of massive verapamil overdose: a case report. J Med Case Reports. 2011 Aug 20;5(1): 399

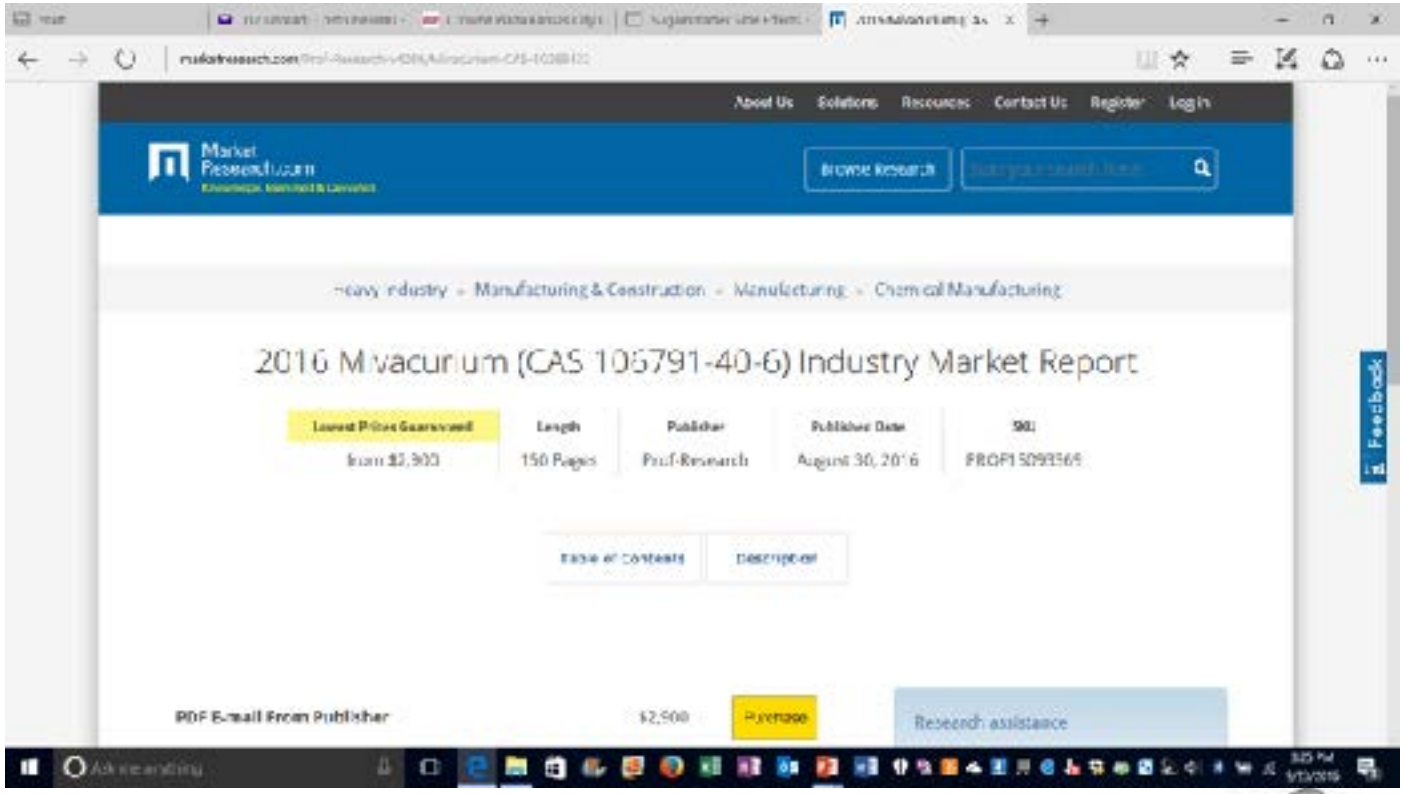
Jovic-Stosic J, Gligic B, Putic V, Brajkovic G, Spasic R. Severe propranolol and ethanol overdose with wide complex tachycardia treated with intravenous lipid emulsion: a case report. Clin Toxicol (Phila). 2011 Jun;49(5):426-30.

Shih YH, Chen CH, Wang YM, Liu K. Successful reversal of bupivacaine and lidocaine-induced severe junctional bradycardia by lipid emulsion following infraclavicular brachial plexus block in a uremic patient. Acta Anaesthesiol Taiwan. 2011 Jun;49(2):72-4.

Pre-operative Alvimopan (Entereg)

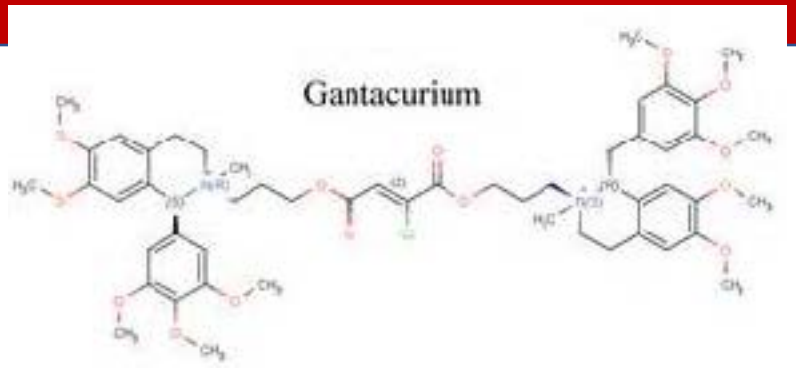


Mivacurium is coming back…



Certified Registered Nurse Anesthetist

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

Release

The U.S. Food and Drug Administration today approved Bridion (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.

"Bridion provides a new treatment option that may help patients recover sooner from medications used for intubation or ventilation during surgery," said Sharon Hertz, M.D., director of the Division of Anesthesia, Analgesia and Addiction Products in the

Inquiries

Media

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The Official Journal of the Anesthesia Patient Safety Foundation

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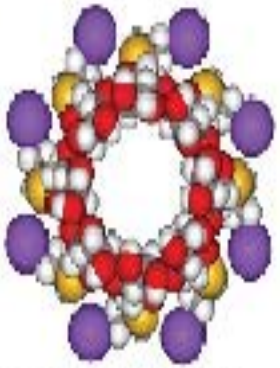
February 2016

The Development and Regulatory History of Sugammadex in the United States

by Glenn Talaycky, MD

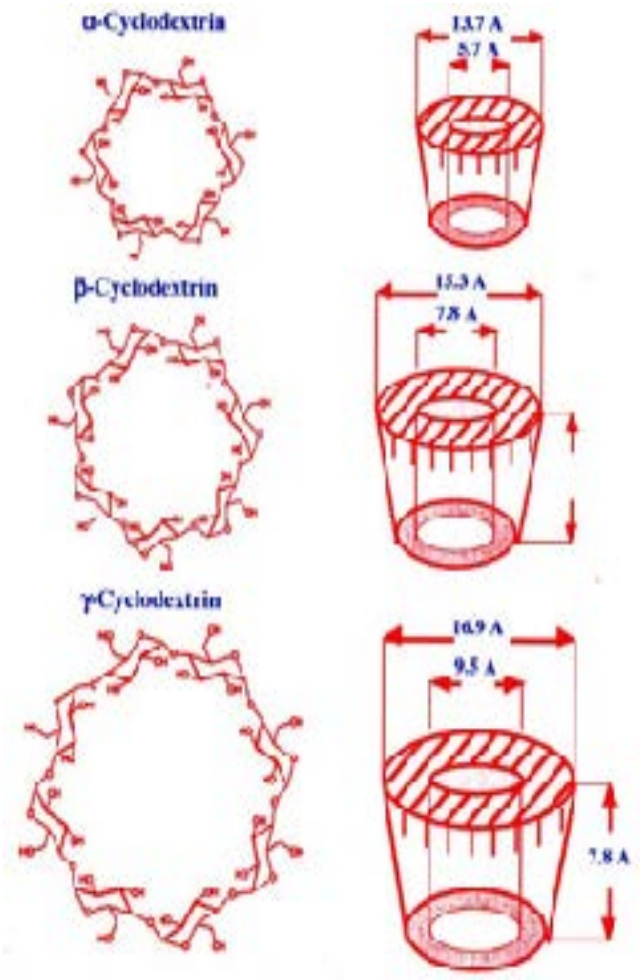
The Neuromuscular Research Group at Organon Laboratories Scotland (east of Glasgow) had been working on the development of fast-onset, short-acting nondepolarizing steroidal neuromuscular blocking agents since the 1960s, which led to the development of pancuronium, vecuronium and rocuronium. Shortly after the launch of rocuronium, questions arose about a possible action of rocuronium on smooth muscle neurotransmission, so Dr. Anton Bom was contacted. Dr. Bom was performing smooth muscle studies at the same research site. Rocuronium is not very water soluble, so buffer solutions with a pH of 4 are required. Dr. Bom attempted to dissolve rocuronium in organic solvents that were traditionally used for smooth muscle studies, none of which were able to solubilize rocuronium. Next, he decided to examine cyclodextrins, which were demonstrated to dissolve steroidal hormones. Cyclodextrins are rigid, ring-shaped molecules composed of sugar units. The outside of the cyclodextrin is hydrophilic, which makes the molecule water soluble. The hole in the middle of the cyclodextrin ring is hydrophobic, which allows lipophilic molecules, like steroids, to enter this cavity, creating water soluble complexes.[1]



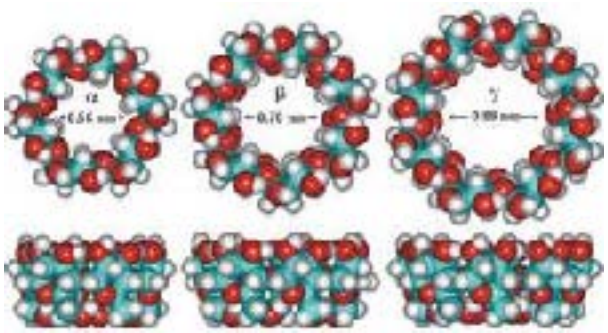
Space-filling model of sugammadex sodium

Since rocuronium has a steroidal nucleus, Dr. Bom speculated that rocuronium would form complexes with cyclodextrins. This binding would prevent rocuronium from acting on the nicotinic acetylcholine receptor and allow rapid reversal of neuromuscular

CYCLODEXTRINS



Cyclodextrins are poly saccharide compounds that were analyzed as scavenging molecules for toxins and additives for food materials

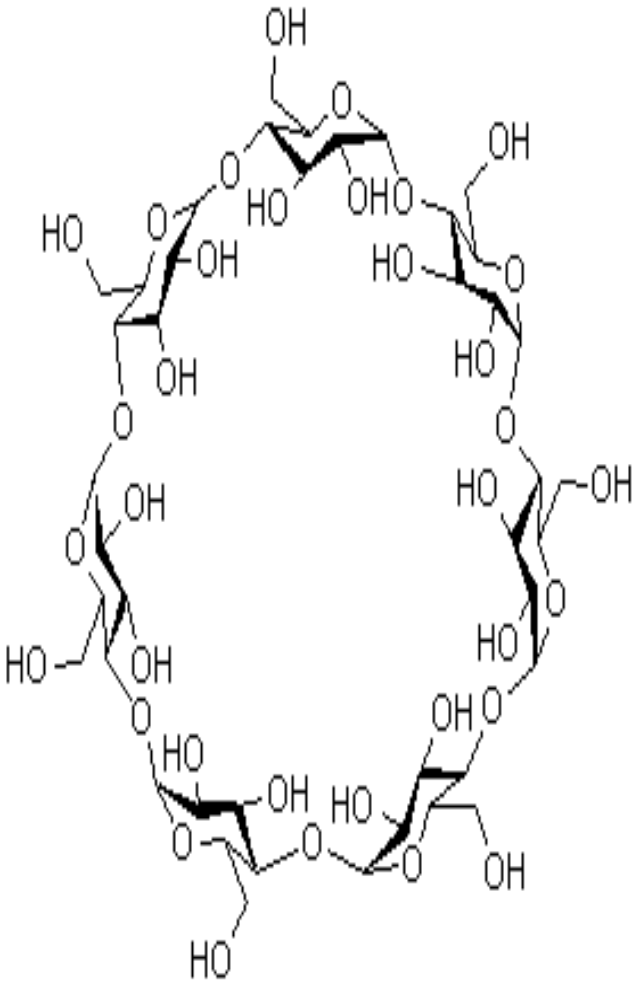


Certified Registered Nurse Anesthetist

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

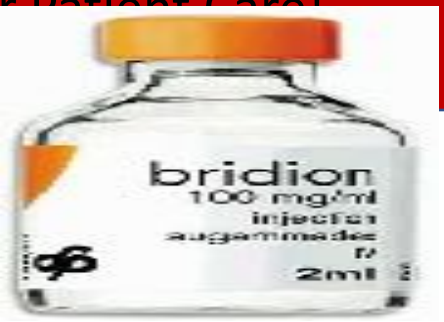
- Forms a very tight water soluble complex with steroidal NDMR
- i.e. ROC > VEC > PANC

- 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.

Sugammadex



- Does not affect SUXX or benzylisoquinoliniums;
- 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

- 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
  - 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??

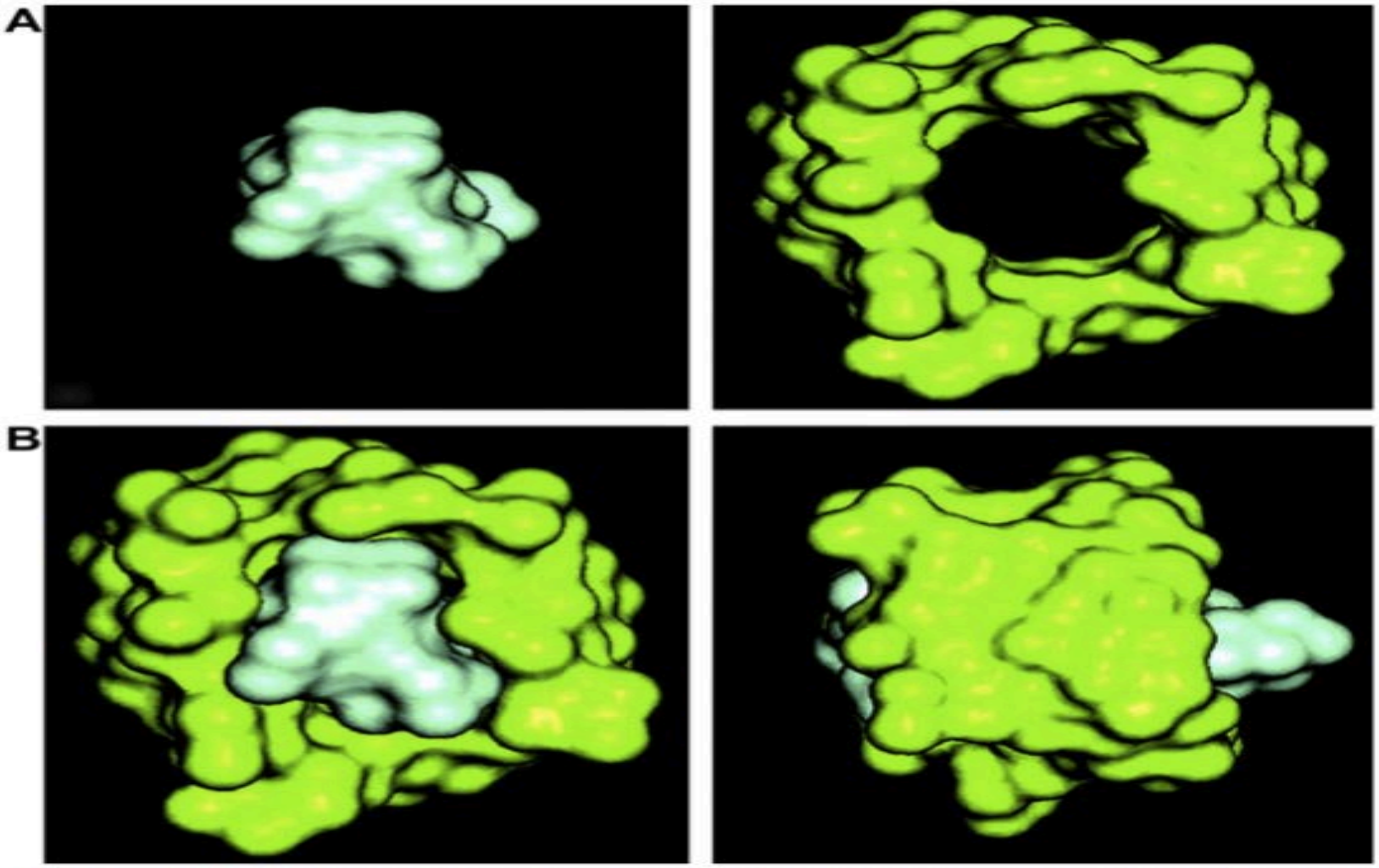


Fig. 5. (*A*) Current Radiograph crystal structure of a rocuronium molecule and a sugammadex molecule. (*B*) Synopsis encapsulation of rocuronium molecule (*blue*) by a sugammadex molecule (*green*) at 1:1 ratio. (*From* Cameron KS, Clark JK, Cooper A, et al. Modified gamma-cyclodextrins and their rocuronium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

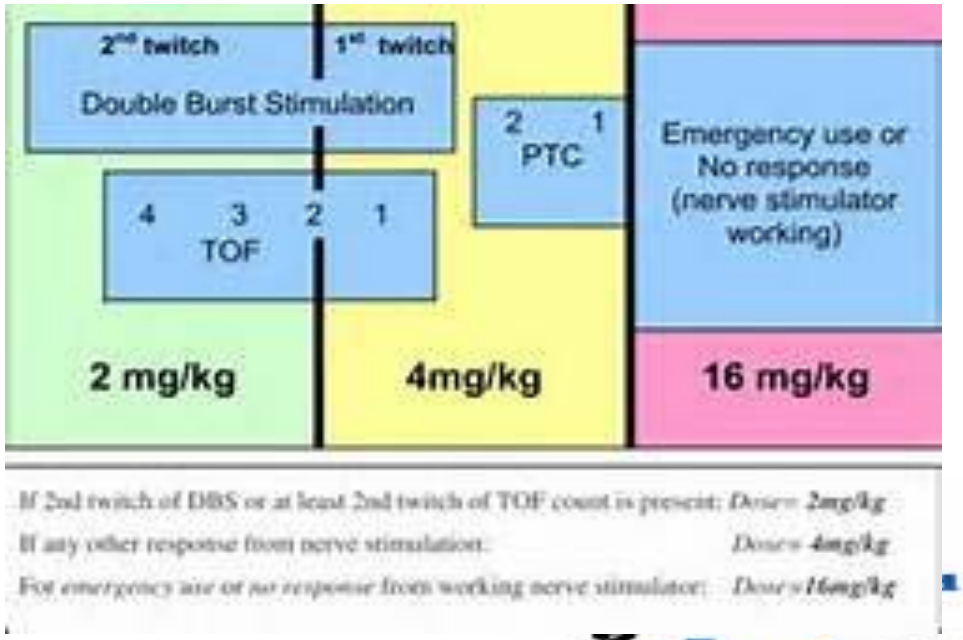
Source: Full Prescribing Information, Bridion® (Sugammadex). 2015, Merck Sharpe and Dohme Corp.
Akha AS et al. Sugammadex: Cyclodextrins, Development of Selective Binding Agents, Pharmacology, Clinical Development, and Future Directions. Anesthesiology Clin 28 (2010) 691-708

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

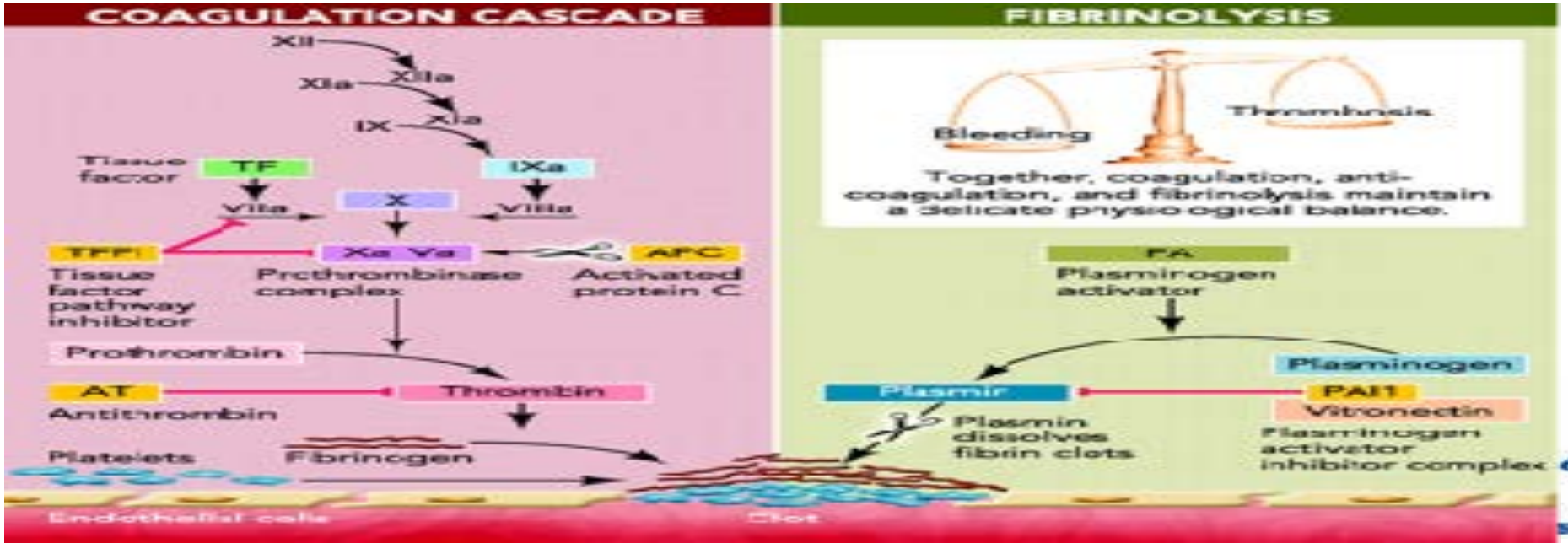
- Serious but rare:
  - Anaphylaxis
  - Bradycardia
- > 10%
  - Nausea, Vomiting, Pain, Hypotension, Headache
- Signs of emergence (moving, sucking, chewing)

- Large meta-analysis with > 1500 patients = no significant difference in side effects compared with neostigmine with less residual paralysis

PT and PTT

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



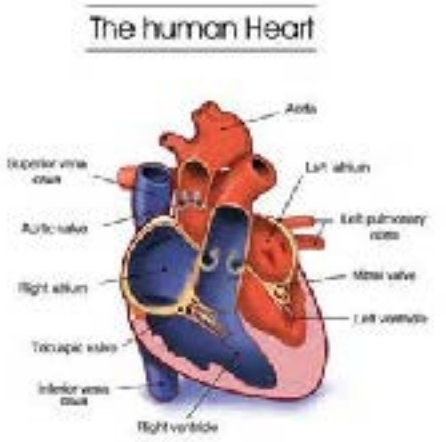
Sugammadex - Bleeding

- 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

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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 Warns!

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!!

Package insert

Merck:

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.

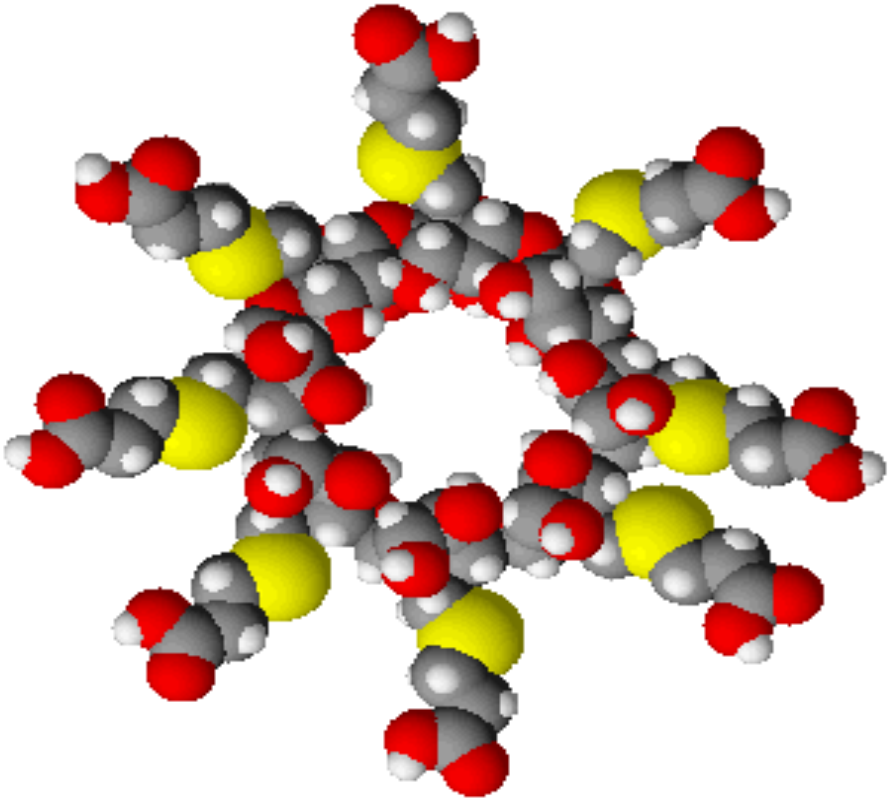
Always Aware

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.

Sugammadex



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Perioperative Medicine | July 2009

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

Zeev N. Kain, M.D., M.B.A.; Jill E. MacLaren, Ph.D.; Leslie Herrmann, B.S.; Linda Mayes, M.D.; Abraham Rosenbaum, M.D.; Justin Hata, M.D.; Jerrold Lerman, M.D., F.R.C.P.C., F.A.N.Z.C.A.

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Anesthesiology 7 2009, Vol.111, 44-49.
doi:10.1097/ALN.0b013e3181a91870

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9:51 PM 10/4/2016

Antidote to Factor X inhibitors

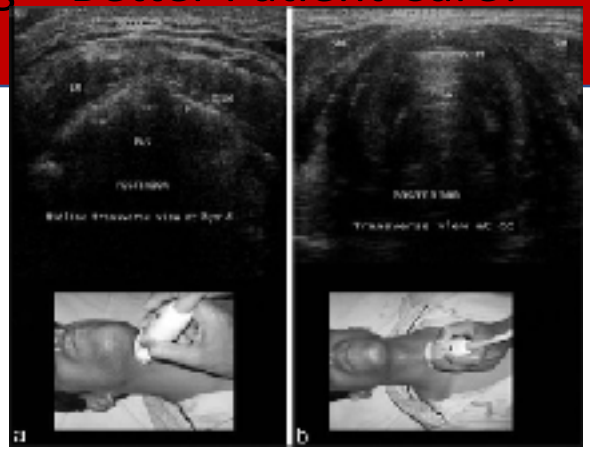
Portola Pharmaceuticals (Nasdaq:PTLA) today announced that **andexanet alfa**, a U.S. Food and Drug Administration (FDA)-designated breakthrough therapy, has been granted orphan drug designation by the FDA's Office of Orphan Products Development for reversing the anticoagulant effect of direct or indirect 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.

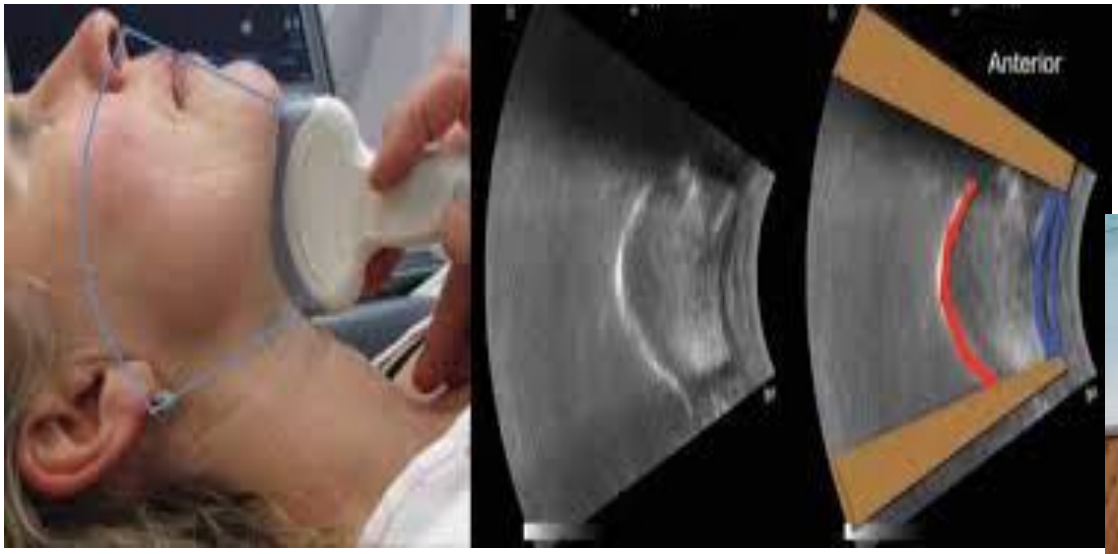
Praxbind (idarucizumab) for use in patients who are taking the anticoagulant Pradaxa (dabigatran) during emergency situations when there is a need to reverse Pradaxa's blood-thinning effects.

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.

New Ultrasound?---

”Another tool to distinguish us from the CRNA”





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A Powerful New Tool for Airway Management

Michael Seltz Kristensen, MD

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Graduate Medical School, Singapore

Others that might impact Anesthesia

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

Just FDA approved:

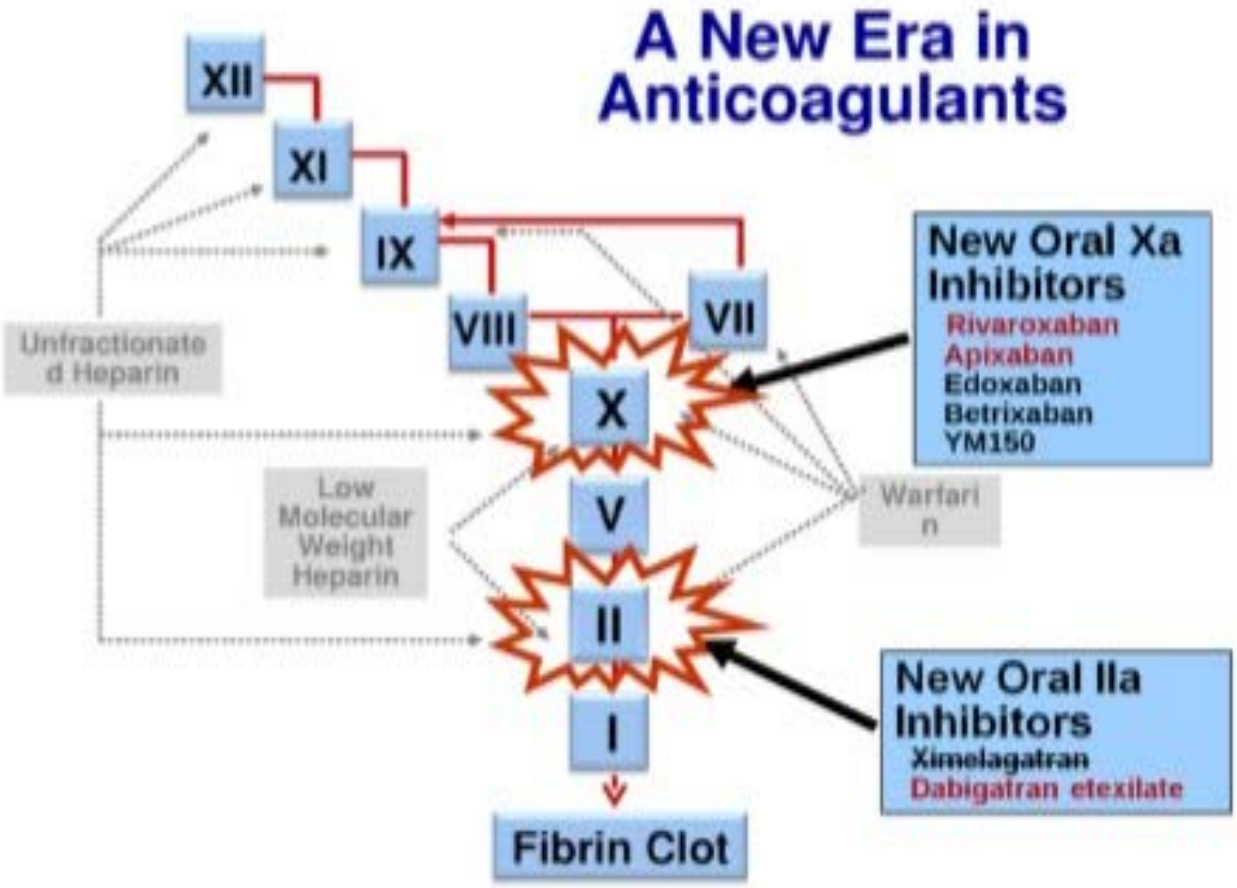
Idarucizumab to reverse pradaxa

Factor X concentrate

RE-VERSE AD™

Study of reversal effects of idarucizumab in patients on active dabigatran

Mechanism of action



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… my brain is full !

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