

New Methods for Analgesia Delivery

Guy Ludbrook MBBS PhD FANZCA

Royal Adelaide Hospital and University of Adelaide
South Australia



Pain and Anaesthesia Research Clinic (PARC)

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Pain and Anaesthesia Research Clinic (PARC)

PARC is a University based research group conducting pharmacological research into Anaesthesia and Pain Medicine. The unit was founded by Professors Guy Ludbrook (Anaesthesia) and Paul Rolan (Clinical Pharmacology) of the University of Adelaide, because of their complementary extensive clinical research expertise.

The purpose of the Unit is not only to undertake contract clinical research for the pharmaceutical industry, but also to provide a safe and suitable environment for the conduct of academic clinical pharmacology studies especially with compounds of narrow therapeutic index such as opioids.

The Unit provides training and employment in pharmaceutical research for local graduates. PARC operates a six bedded clinical research unit within the Royal Adelaide Hospital (RAH). The RAH is the major teaching hospital in Adelaide, South Australia. It is adjacent to the University of Adelaide campus.

PARC is a business unit of Adelaide Research & Innovation (ARI), the commercial arm of the University of Adelaide.

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Anesthesia for the 21st century

Theodore H. Stanley, MD^{✉1}

¹From the Department of Anesthesiology, University of Utah Health Sciences Center, Salt Lake City.

[✉]Corresponding author.

“Anesthesiology is on the verge of a major evolution that will involve newer, safer, and simpler techniques to deliver these agents.”

“The new routes and delivery systems promise....”

Proc Bayl Univ Med Cent 13(1) 7-10, 2000

Anesthesia for the 21st century

Theodore H. Stanley, MD^{✉1}

¹From the Department of Anesthesiology, University of Utah Health Sciences Center, Salt Lake City.

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- ✓ improved convenience
- ✓ improved safety
- ✓ increased effectiveness
- ✓ increased bioavailability
- ✓ continuous delivery with fewer peaks and valleys
- ✓ decreased side effects
- ✓ decreased dosage and frequency of administration
- ✓ decreased cost

Anesthesia for the 21st century

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Context of perioperative analgesia

Limited to existing opioids and local anaesthetics

Look for genuine improvements in care

- how is success judged, and by whom?

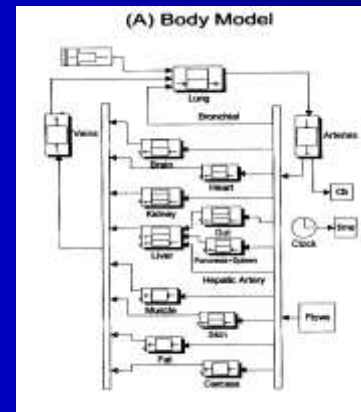
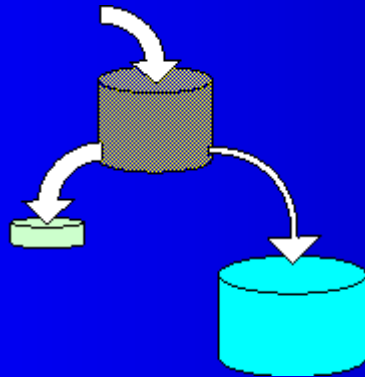
Intravenous drug administration

Usually most direct route to target receptor

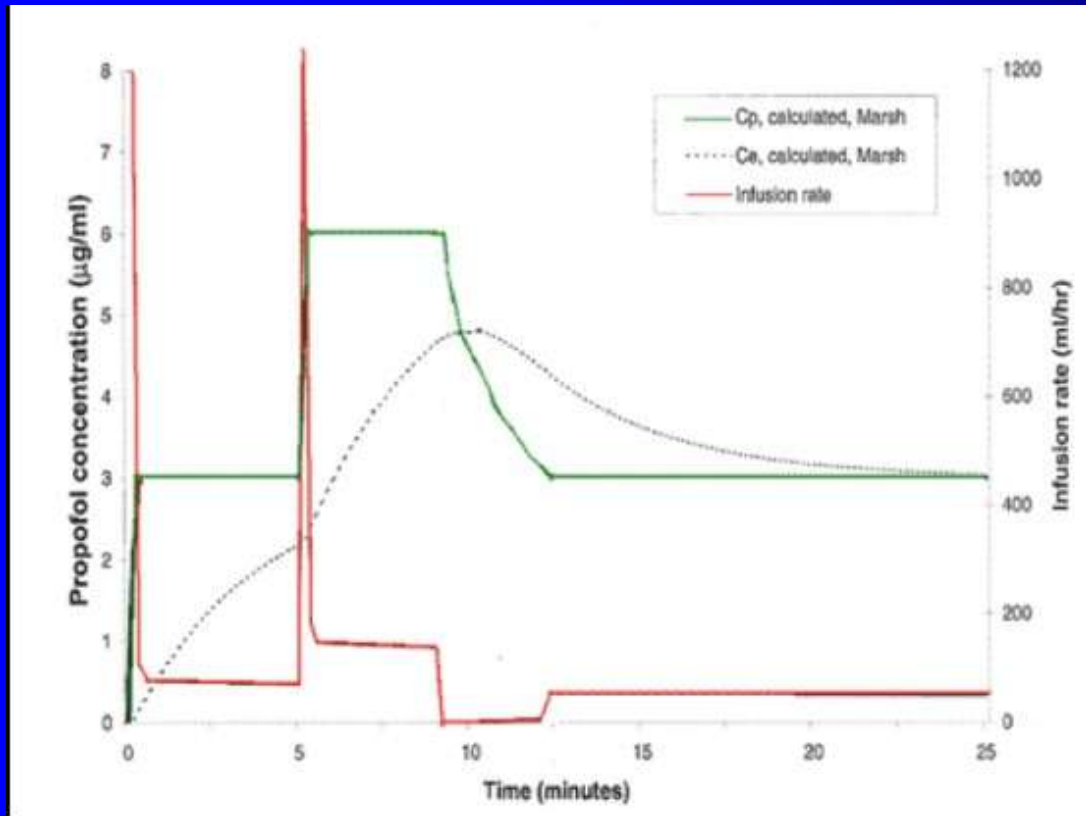
Requires i.v. access

Must account for basic pharmacokinetics

Must account for inter-individual variability



Intravenous drug administration computer-assisted administration






Diprifusor
Remifusor

Cochrane systematic review of data

Target-controlled infusion versus manually-controlled infusion of propofol for general anaesthesia or sedation in adults

Leslie K, Clavisi O, Hargrove J

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Plain Language Summary

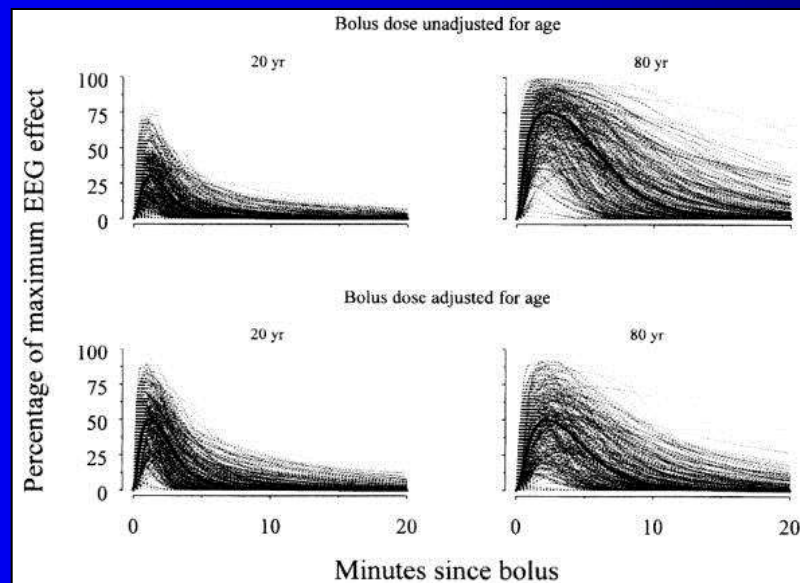
Computer-controlled delivery versus manual delivery of propofol to produce general anaesthesia or sedation in adult patients

Continuous infusions of the intravenous anaesthetic propofol are commonly used to induce and maintain sedation and general anaesthesia. Propofol may be administered by a computer-controlled (target-controlled) or manually-controlled delivery system. Randomized trials have explored the differences in quality of anaesthesia, adverse event rate and propofol drug cost between the two types of delivery systems but their comparative effectiveness remains controversial. As computer-controlled delivery systems are in widespread international use, and potentially may be more expensive without added benefit, a systematic review of randomized controlled trials was warranted. After a search of the literature, 20 randomized controlled trials (RCTs) involving 1759 patients were selected for review. Eighteen studies focused on general anaesthesia and two studies focused on sedation. All papers were of poor methodological quality and there was high variability in the way outcomes were defined, measured and reported. Overall, target controlled infusion (TCI) was associated with higher total doses of propofol than manually controlled infusion (MCI), resulting in marginally higher propofol drug costs. However, fewer dose adjustments (interventions) were required by the anaesthetist during the use of TCI compared with MCI. With regard to quality of anaesthesia, recovery or adverse events (hypotension, apnoea, movement during anaesthesia), no clinically significant differences were demonstrated between treatment arms. No cases of unintentional awareness were reported. Effect size for total dose, induction dose, induction time, time to eye opening and movement during anaesthesia were highly variable because these outcomes depended on the infusion regimen used, which was different for every study. This systematic review does not provide sufficient evidence to make firm recommendations about the use of TCI versus MCI in clinical anaesthetic practice.

“This systematic review does not provide sufficient evidence to make firm recommendations about the use of TCI versus MCI...”

Drug unpredictability

“A dose which may be barely adequate for a certain patient may easily be an overdose for another.”



RC Adams, Can Med Assoc J. April 330-337, 1938
C Minto et al., Anesthesiology. 86(1):24-33 1997

Target-Controlled Infusion for Remifentanyl in Vascular Patients Improves Hemodynamics and Decreases Remifentanyl Requirement



Table 2. Hemodynamic Events

	Group I, RIVA	Group II, TCIR	P value
Patients with at least 1 intraoperative episode			
<u>Hypotension</u>	16	6	<0.001
Hypertension	0	2	0.08
Tachycardia	0	0	
Bradycardia	0	1	0.16
Patients receiving intraoperatively			
Ephedrine	19	19	0.50
Neosynephrine	13	10	0.19
Patients receiving during recovery			
Nicardipine administration	14	9	0.07
β -Blockers administration	16	10	0.04
Need for morphine titration	4	3	0.34

RIVA = continuous intravenous weight-adjusted infusion of remifentanyl, TCIR = target-controlled infusion for remifentanyl.

Manual Versus Target-Controlled Infusion Remifentanil Administration in Spontaneously Breathing Patients

Annelies T. Moerman, MD ^{*}, Luc L. Herregods, MD, PhD ^{*},
Martine M. De Vos, MD, PhD [†], Eric P. Mortier, MD, Dsc ^{*‡} and
Michel M. R. F. Struys, MD, PhD ^{‡§}

.... a lower incidence in apnea and respiratory depression (TCI $n = 7$, MCI $n = 16$, $P < 0.05$) ...

Anesth Analg 108(3) 828-834, 2009

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Intraoperative measurement of analgesia

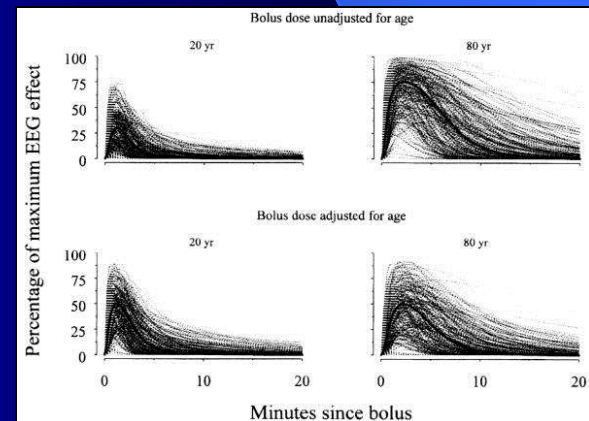
Pupillometry

Response indices

EMG

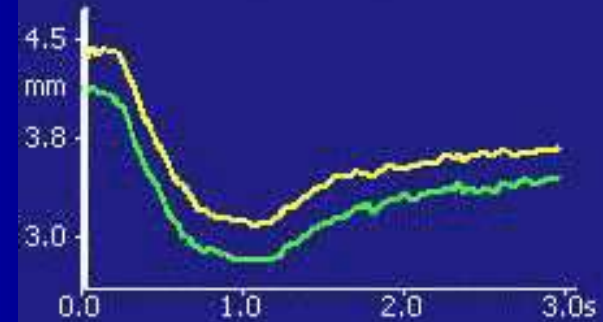
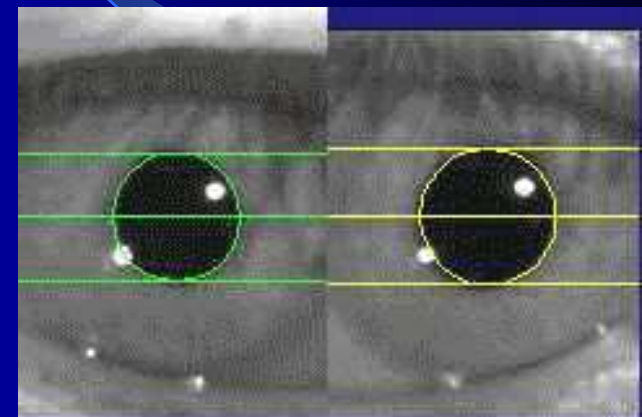
EEG

Heart rate/plethysmography



Pupillometry

The screenshot shows the NeuroOptics website interface. At the top, the logo reads "NEUROPTICS From Pupil to Expert... Precision Guaranteed." Below the logo is a navigation bar with links for Home, Critical Care, Ophthalmology, Research Applications, Dark Pupil Library, and About Us. The main content area features a "Critical Care" section with a video player. The video shows a healthcare professional using the NeuroOptics NPI-100 Pupilometer on a patient in a hospital bed. A monitor in the background displays vital signs, including a heart rate of 78. Text on the video player reads "The NeuroOptics NPI-100 Pupilometer for Critical Care" and "NEUROPTICS". A link below the video says "Click here to watch full length video".



Playing...

Response index - EMG

British Journal of Anaesthesia 107 (5): 710–18 (2011)
Advance Access publication 28 July 2011 · doi:10.1093/bja/aer228

BJA

CRITICAL CARE

Responsiveness of the frontal EMG for monitoring the sedation state of critically ill patients

T. S. Walsh^{1*}, T. P. Lapinlampi², P. Ramsay¹, M. O. K. Särkelä², K. Uutela² and H. E. Viertiö-Oja²

¹ Anaesthetics, Critical Care and Pain Medicine, General Intensive Care Unit, Edinburgh Royal Infirmary, Little France Crescent, Edinburgh EH16 4SA, UK

² GE Healthcare Finland Oy, Kuortaneenkatu 2, FI-00510 Helsinki, Finland

* Corresponding author. E-mail: twalsh@staffmail.ed.ac.uk

“.... a dynamic interaction between the current level of stimulation, the sedation and analgesic state of the patient...”

EMG responses to environment
internal (pain, anxiety)
external (noise, light procedures..)

Pupillometry to guide analgesic doses

	Group H	Group P	p
Intraoperative Remifentanil (microg/kg/h of GA)	8.2 +/- 1.8	3.9 +/- 0.7	< 0.001
Intraoperative Propofol (mg/kg/h of GA)	9.0 +/- 1.2	8.3 +/- 1.1	NS
Total Morphine in PACU at H2 (mg/kg)	0.25 +/- 0.08	0.19 +/- 0.07	0.02
Total Morphine at H12 (mg/kg)	0.35 +/- 0.17	0.23 +/- 0.1	0.01
Total Morphine at H24 (mg/kg)	0.43 +/- 0.23	0.31 +/- 0.2	0.1

“... ..reduces ... remifentanil consumption, and reduced postoperative morphine consumption without increasing the level of postoperative pain.”

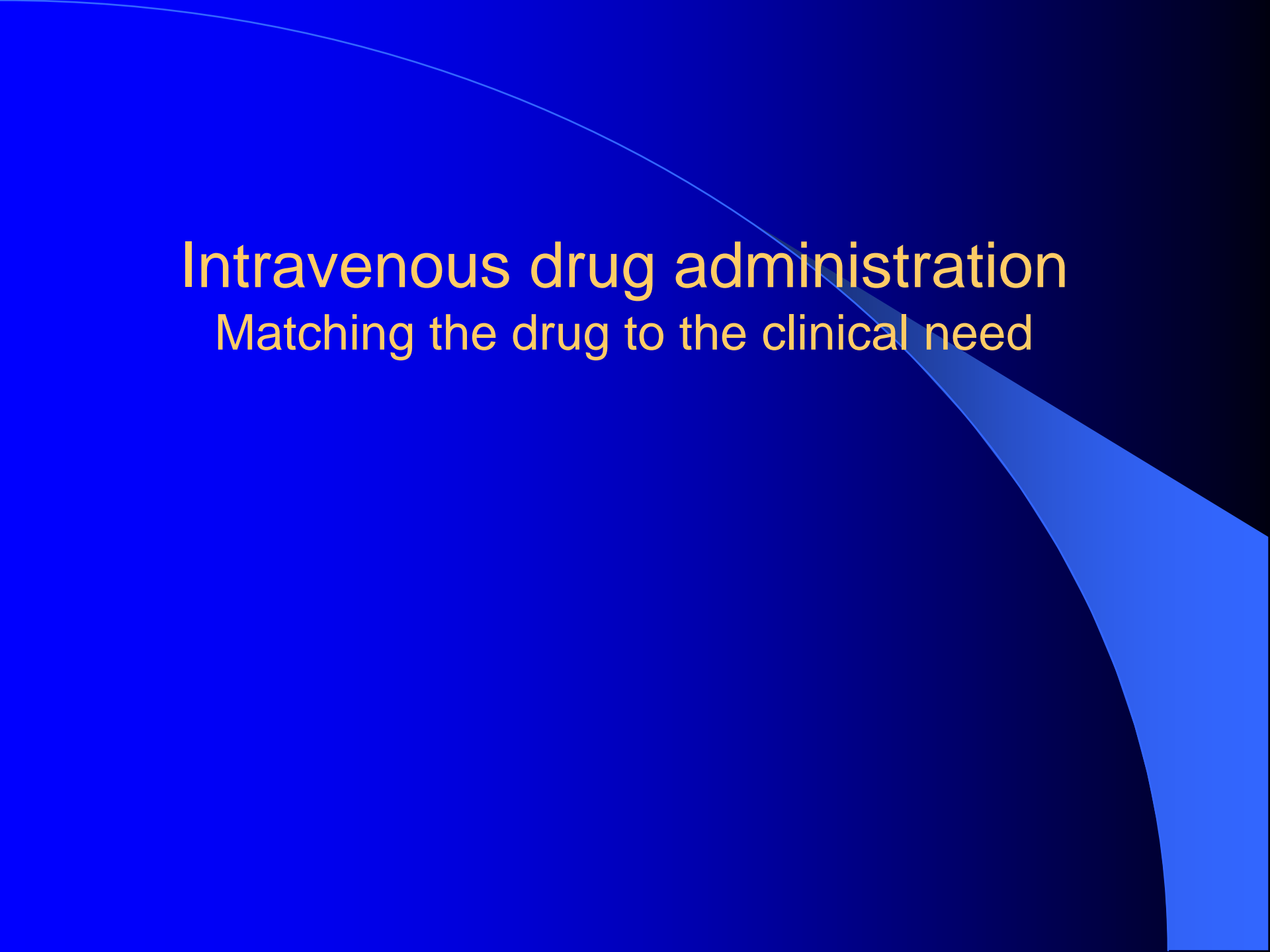
Comparison of Surgical Stress Index-guided analgesia with standard clinical practice during routine general anaesthesia

Xinzhong Chen et al.

Unwanted events

	SSI-guided	Standard practice
hypertension	11*	84
hypotension	5*	67
tachycardia	0	2
bradycardia	23*	111
movements	3*	14
TOTAL	42*	278

Chen et al., Anesthesiology 112:1175-83, 2010



Intravenous drug administration

Matching the drug to the clinical need

ANESTHESIA & ANALGESIA[®]

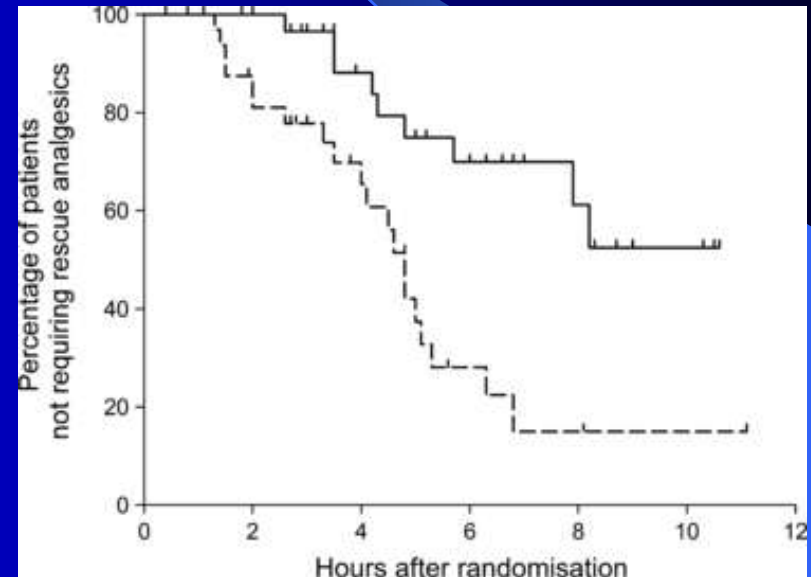
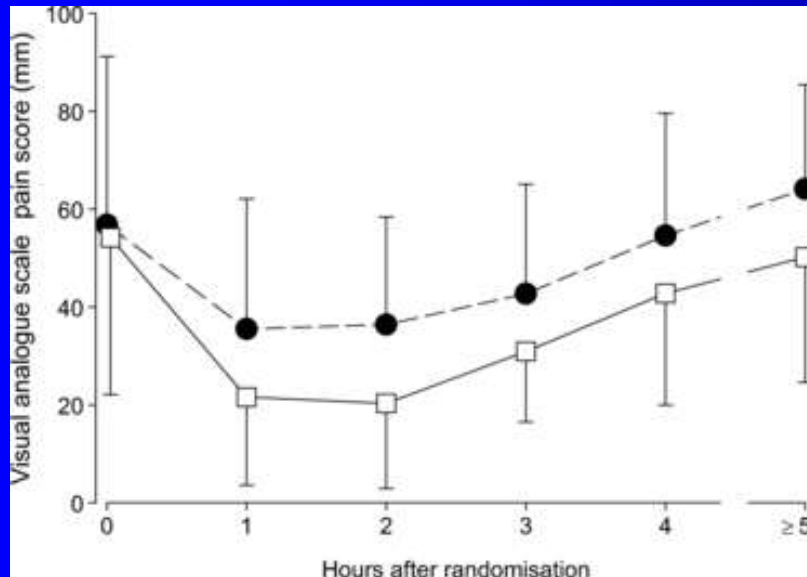
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Use of Remifentanyl for Labor Analgesia: The Good and the Bad

Joel Waring, MD, Sohail K. Mahboobi, MD, Kalpana Tyagaraj, MD and
David Eddi, MD

A double-blind randomised comparison of intravenous patient-controlled remifentanyl with intramuscular pethidine for labour analgesia



Intravenous drug combinations pain protocol in PACU



ET SEVTEO



www.alphajournal.com/issue/2007

	AM group	M group
Time to comfort (min)	32.8 ± 26	40.9 ± 34
Volume to achieve comfort (ml)	15 ± 17	15.2 ± 11
Time to discharge (min)	88.4 ± 55	105.3 ± 75

Results are expressed as mean ± S.D.

Waleed K. Alkhazrajy, Pamela E. Macintyre, Richard N. Upton,
Jennifer Ong*, Guy L. Ludbrook

Intravenous drug combinations patient controlled analgesia

Addition of remifentanyl to patient-controlled tramadol for postoperative analgesia: a double-blind, controlled, randomized trial after major abdominal surgery

H. Unlugenc^{a1 c1}, S. Tetiker^{a1} and G. Isik^{a1}

Comparison of the effect of adding remifentanyl to patient-controlled tramadol or morphine for postoperative analgesia after major abdominal surgery

Hakki Unlugenc, MD
Sibel Tetiker, MD
Selim Büyükkurt, MD
Tayfun Guler, MD
Geylan Isik, MD

European Journal of Anaesthesiology (2008), 25: 968-975
J Opioid Management (2009) 5(5): 247-255

Intravenous drug combinations postoperative PCA

0063

A double-blinded randomized evaluation of alfentanil and morphine versus fentanyl: analgesia and sleep trial ('DREAMFAST').

Angeline Lee¹, Edmond O'Loughlin², Lindy J Roberts¹

¹*Sir Charles Gairdner Hospital, Perth, WA, Australia,* ²*Fremantle Hospital, Perth, WA, Australia*

- ✓ Lower pain scores
- ✓ Less likely to need ketamine supplementation
- ✓ Unchanged sleep disturbance

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Mucosal delivery nasal or sublingual spray

Avoids an i.v.

Reduces first pass extraction

Attractive concept perioperatively?



A Randomized Controlled Trial Comparing Intranasal Fentanyl to Intravenous Morphine for Managing Acute Pain in Children in the Emergency Department

**Meredith Borland, MBBS,
FACEM**

Ian Jacobs, PhD, FRCNA

Barbara King, MBBS, FRACP

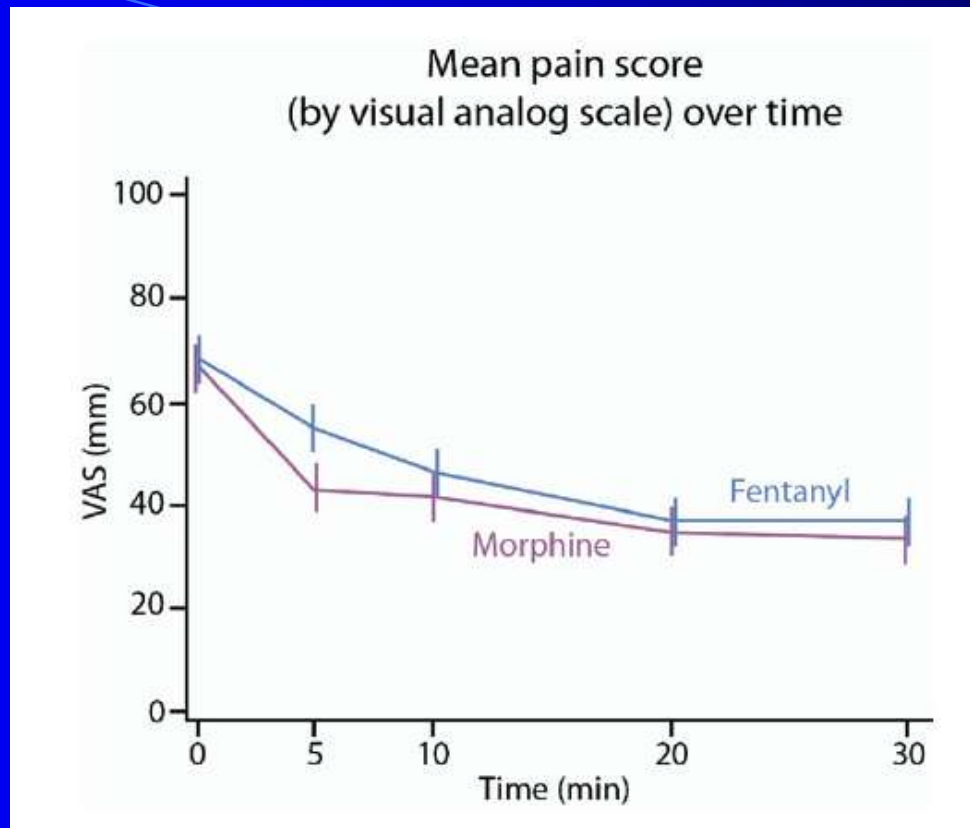
Debra O'Brien, MBBS, FACEM

From the Princess Margaret Hospital for Children, Subiaco (Borland, King); School of Paediatrics and Child Health, University of Western Australia, Perth (King); Discipline of Emergency Medicine, University of Western Australia, Perth (Jacobs); and the Emergency Department, Sir Charles Gairdner Hospital, Nedlands (O'Brien) WA, Australia.



Figure 1. Mucosal Atomiser Device.

Borland et al., *Ann Emerg Med.*
49(3):335-40, 2007



Intranasal fentanyl ... was shown to be an effective analgesic in children when compared to intravenous morphine at 0.1 mg/kg.

Borland et al., Ann Emerg Med. 49(3):335-40, 2007

Pharmacokinetic analysis i.v. versus nasal

Delayed time to C_{max} (13 vs 6 min)

Lower C_{max} (1.2 vs 2.0 ng/mL)

Analgesic effect lagged behind the venous concentration - half-life of 2.5 mins

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Transdermal delivery

No needles

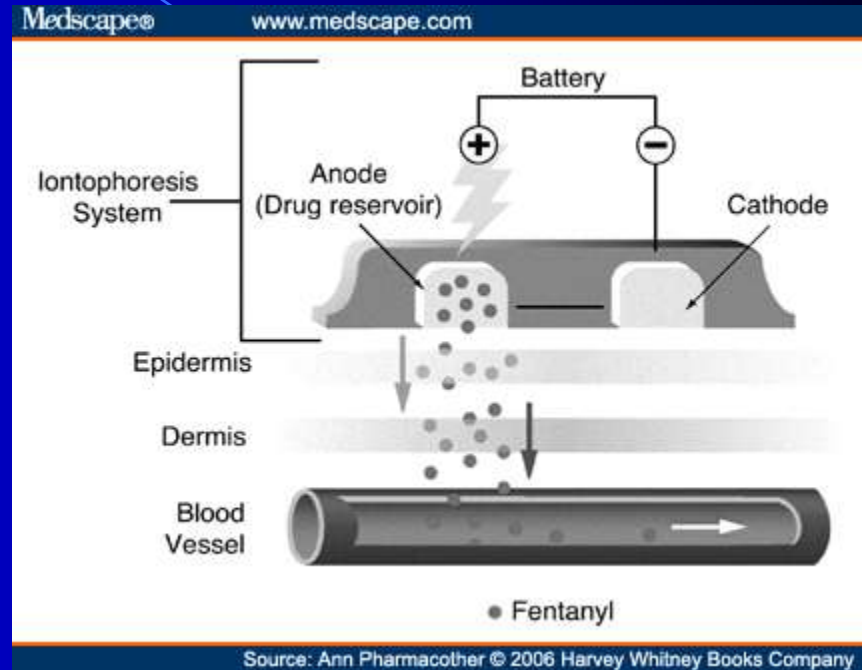
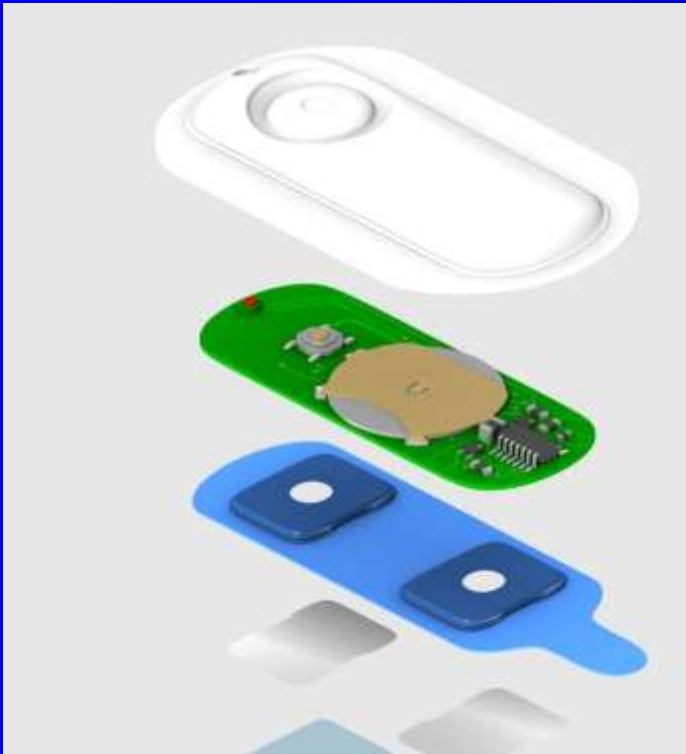
Sustained release

Tough challenge - skin is there for a reason

Technologies

- Iontophoresis
- Nanotechnology
- Other

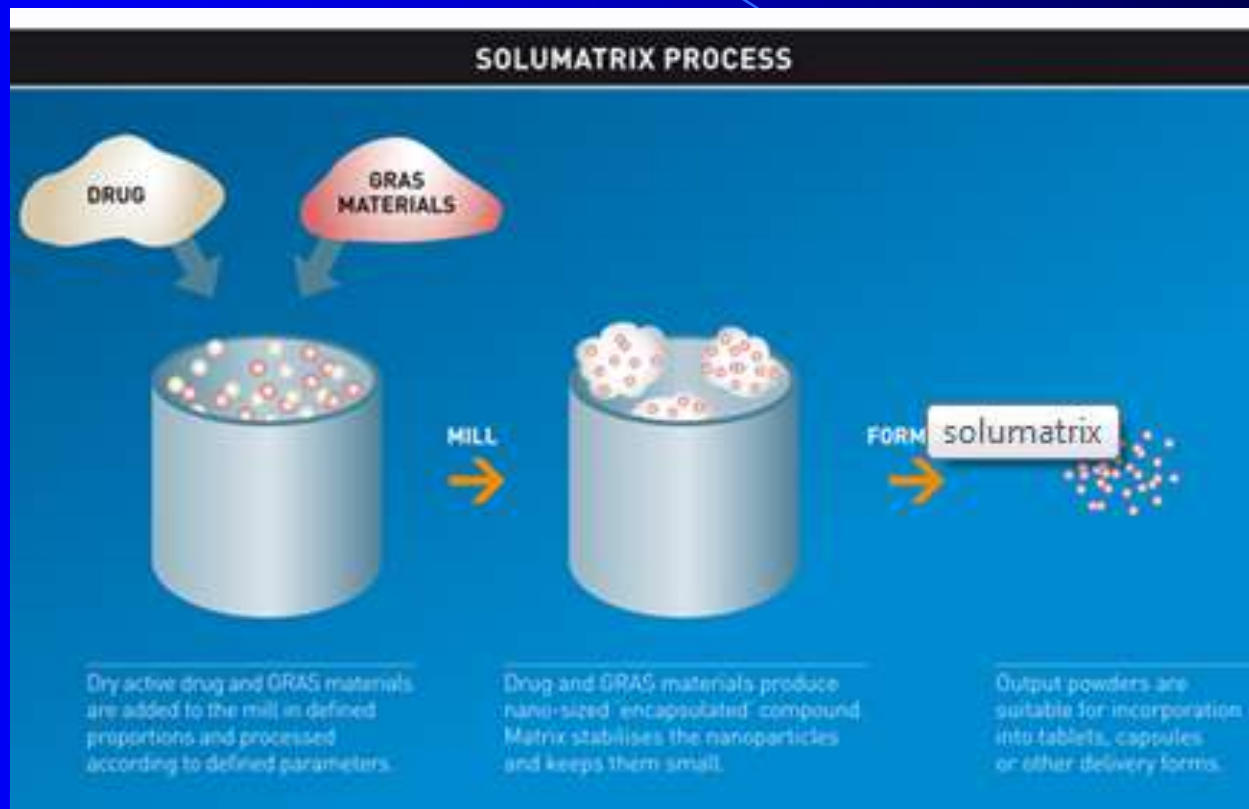
Iontophoresis



Viscusi E R et al. Anesth Analg 2006;102:188-194

ANESTHESIA & ANALGESIA

Nanotechnology



Reducing drug particle size to enhance drug dissolution

iCeutica's proprietary SoluMatrix reformulation platform is a straightforward, scalable manufacturing process that can produce nano-sized drug particles which are 10 to 200 times smaller than conventional drug particles. The particles are generated using the patented SoluMatrix de-milling method, which breaks the drug particles into a very fine powder.



Abstract:

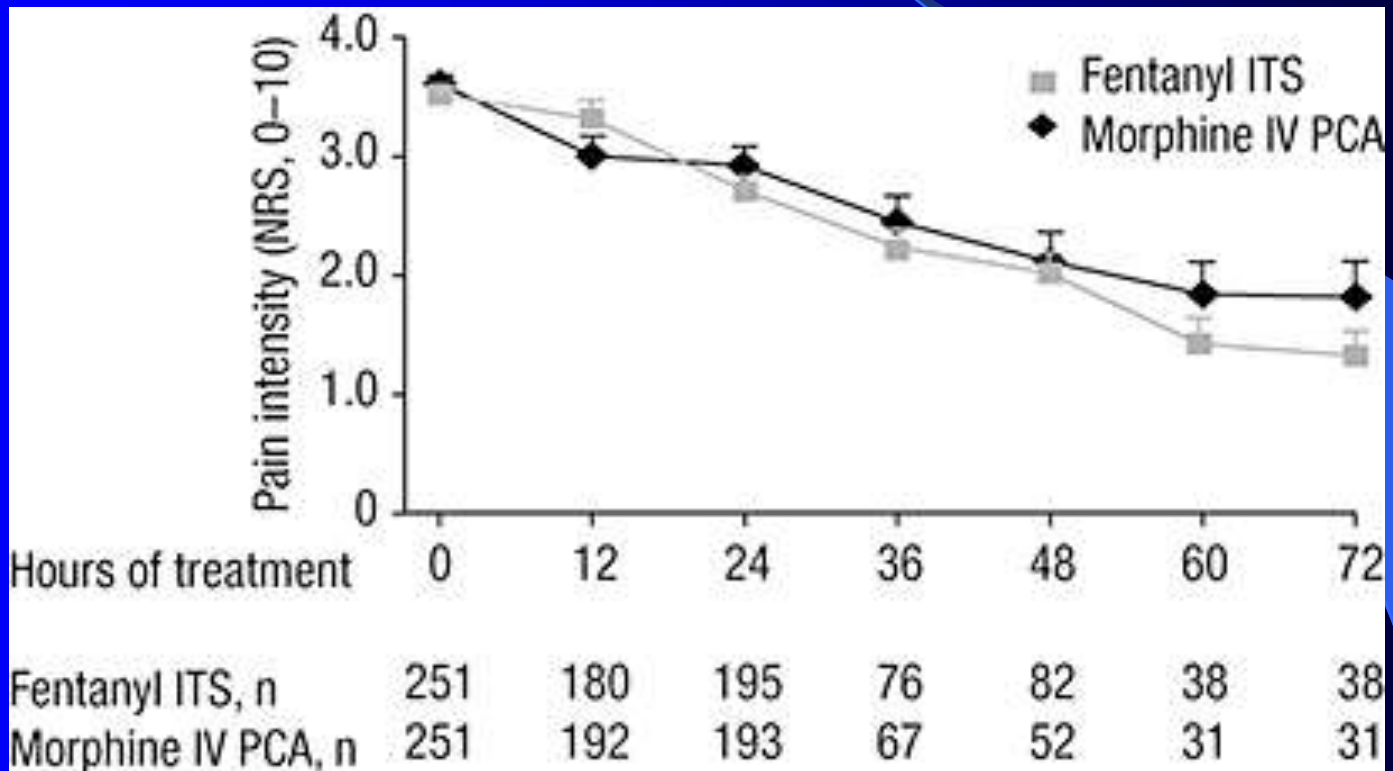
Data from Study of Indomethacin Presented to American Headache Society

Several Novel NSAIDs Being Developed by Iroko Pharmaceuticals

Early Results of Development Program in Nano-Formulated NSAIDs Show Potential for Faster Pain Relief at Lower Doses

Washington, DC | Posted on June 4th, 2011

Efficacy and Safety of the Fentanyl Iontophoretic Transdermal System (ITS) and Intravenous Patient-Controlled Analgesia (IV PCA) with Morphine for Pain Management Following Abdominal or Pelvic Surgery



Minkowitz et al., Am Acad Pain Med 8(8): 657-668, 2007

Efficacy and Safety of the Fentanyl Iontophoretic Transdermal System (ITS) and Intravenous Patient-Controlled Analgesia (IV PCA) with Morphine for Pain Management Following Abdominal or Pelvic Surgery

	PCA	ITS
Ease of use - patients (higher is better)	4.18	4.47
Ease of use - nurses (lower is better)	1.09	0.47

ANESTH ANALG
1993;77:61-6

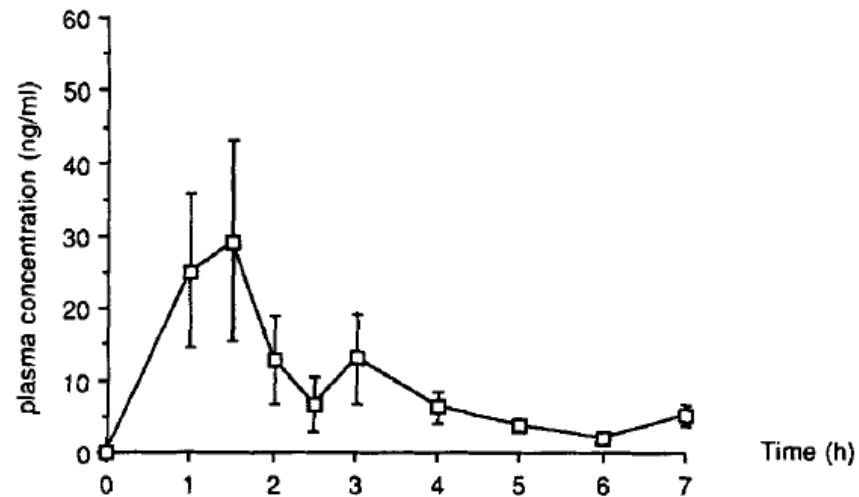


Figure 1. Mean fentanyl plasma concentrations versus time after iontophoresis performed for 1 h (0.17 mA/cm^2 direct current) in rat. Fentanyl ($40 \text{ } \mu\text{g/mL}$) was introduced in a citrate buffer pH 5 (0.01 M) ($n = 9$).

Spray on fentanyl



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Steady-state pharmacokinetics of fentanyl after administration of a novel non-occlusive transdermal system.

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Supportive Care

Category:
Patient and Survivor Care

Meeting:
2005 ASCO Annual Meeting

Session Type and Session Title:
This abstract will not be presented at the 2005 ASCO Annual Meeting but has been published in conjunction with the meeting.

Abstract No:
8199

Citation:
Journal of Clinical Oncology, 2005 ASCO Annual Meeting Proceedings. Vol 23, No. 16S, Part I of II (June 1 Supplement), 2005: 8199

Author(s):
C. Stone, A. J. Humberstone, K. Gardner, A. Evans, D. Shaw, G. L. Ludbrook

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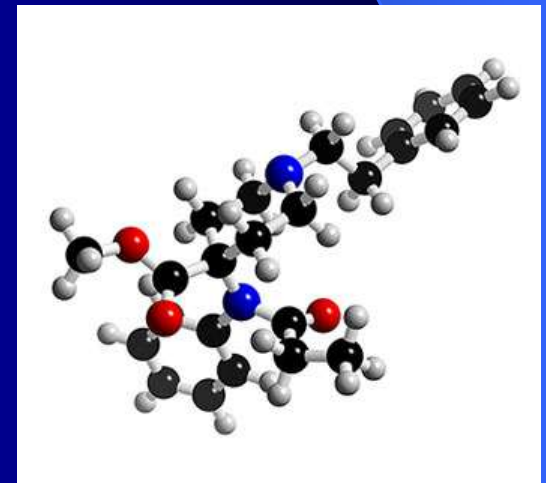
Moscow Theatre hostage crisis

23 October 2002

40 to 50 armed Chechens took 850 hostages

Russian Spetsnaz forces pumped something into the building's ventilation system

39 of the attackers were killed by Russian forces, along with at least 129 of the hostages



Slow release formulations

Opioids and Local anaesthetic

Placement

Wound

Joints

Epidural space

Large nerves

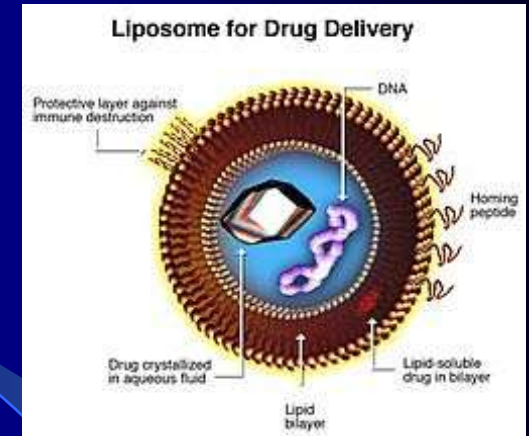
Encapsulation technology

Liposomes

Cyclodextrins

Vesicles

DepoFoam(TM)



Lipid-based particles containing discrete water-filled chambers containing active drug

10-30 microns in diameter and are suspended in saline

The particles deliver their drug payload over a period that can be modified from 1 to 30 days

Abstract ID: A47

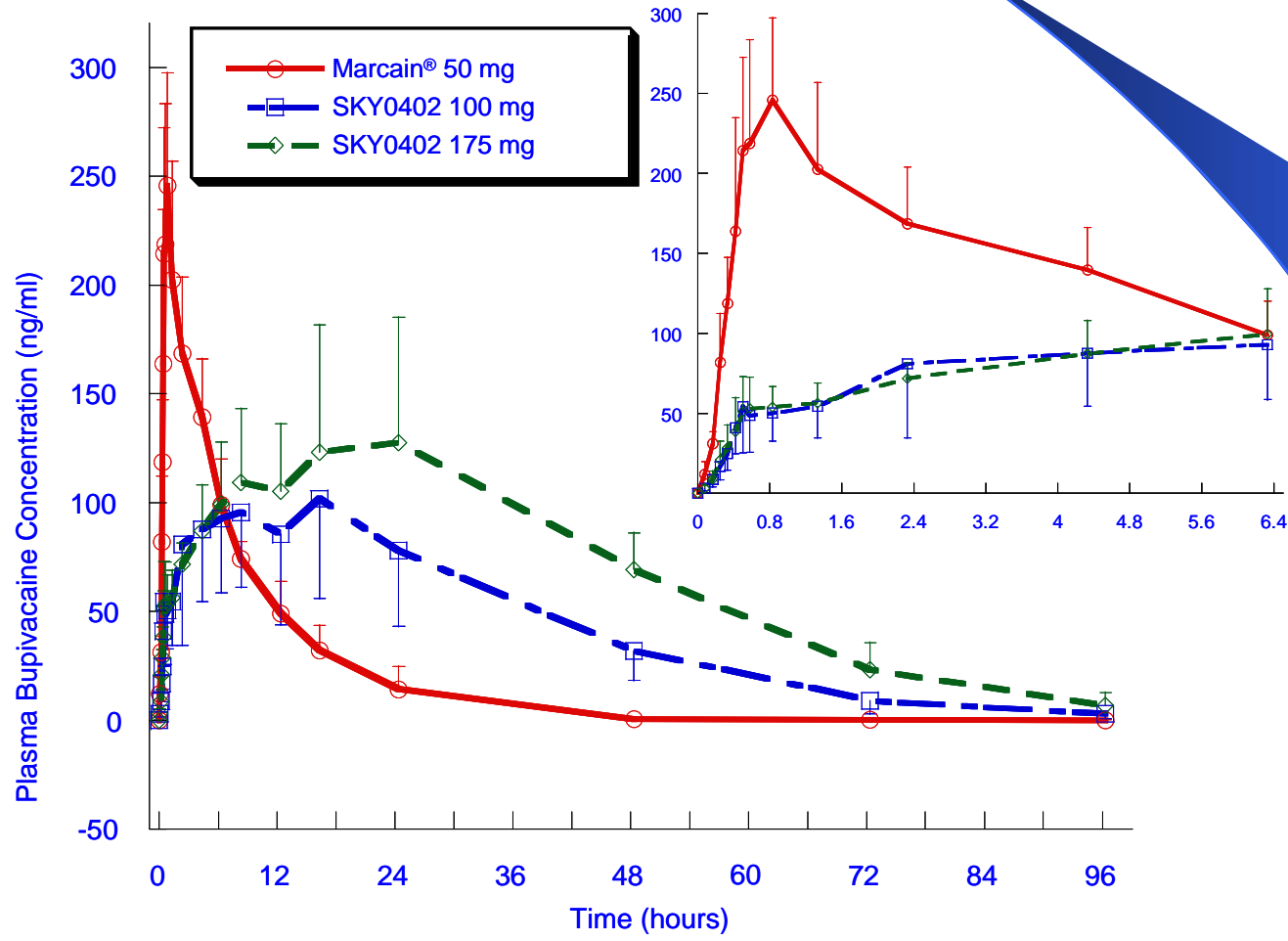
The Pharmacokinetic Profile of an Extended-Release Liposomal Formulation of Bupivacaine Administered via a Single Epidural Injection

Authors: Ludbrook G1, Ardeleanu M2, Manvelian G3, Rashti N4

University of Adelaide Adelaide South Australia Australia 1, SkyePharma Inc. San Diego CA USA2, SkyePharma Inc. San Diego CA USA3, SkyePharma Inc. San Diego CA USA4

Reg Anesth Pain Med 2005; 30(3):A47

Figure 1: Mean (SD) Bupivacaine Plasma Concentrations



**High-Dose Bupivacaine Remotely
Loaded into Multivesicular Liposomes
Demonstrates Slow Drug Release Without
Systemic Toxic Plasma Concentrations
After Subcutaneous Administration in
Humans**



Davidson E M et al. *Anesth Analg* 2010;110:1018-1023

Haemorrhoids



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Clinical Anesthesiology

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Bupivacaine Formulation Extends Local Relief

by Dave Levitan

A randomized study of 100 patients undergoing hemorrhoidectomy found that a slow-release formulation of bupivacaine resulted in significantly longer local analgesia and decreased need for opioid rescue medication compared with plain bupivacaine.

The search for a viable long-acting anesthetic has been a frustrating one, said study co-author Paul F. White, PhD, MD, director of clinical research at Cedars-Sinai Medical Center in Los Angeles. "There have been multiple attempts, and for whatever reason it has proven to be much more difficult than anyone imagined."

The liposomal formulation, called Exparel (Pacira Pharmaceuticals), uses the DepoFoam carrier of bupivacaine and releases the drug more slowly, allowing for longer analgesia. "Instead of having a six- to eight-hour half-life, as bupivacaine usually does, it extends its half-life to two to three days," said Dr. White, a member of the *Anesthesiology News* editorial board. DepoFoam is already a component of other slow-release drugs, including Pacira's morphine product DepoDur, and Exparel has shown promise in other Phase II and III studies.

Shoulder repair

The screenshot shows the Drugs.com website interface. At the top left is the Drugs.com logo with the tagline "Drug Information Online". To the right is a search bar with the placeholder text "enter a search term". Below the search bar is a navigation menu with tabs for "Drugs A-Z", "Pill Identifier", "Interactions Checker", "News / Alerts", "Health Professionals", and "Commur". Underneath the navigation menu are links for "FDA Drug Alerts", "Consumer News", "Industry News", "New Drugs", "Pipeline", "Clinical Trial News", "Get News via RSS", "Twitter", "Blog", and "FDA Label". The main content area shows a breadcrumb trail: "Home > News > Clinical Trials". To the right of the breadcrumb trail are links for "Print", "Save", and "Share". Below the breadcrumb trail is the main article title: "DURECT Reports Data From European Phase IIb Shoulder Study of Posidur) (SABER-Bupivacaine) and Amendment of the Nycomed Agreement". To the right of the article title is a "Sign In or Register" box with a "username" input field. Below the article title are three advertisements by Google. The first advertisement is titled "55/YO Mum Looks 35" and includes the URL "www.CollagenRenew.net/Anti_Wrinkles" and the text "Mum Reveals Shocking Trick for Erasing Wrinkles! Doctors Hate Her". The second advertisement is titled "Trifecta Multimedical" and includes the URL "www.TrifectaMultimedical.com" and the text "Online Investigator Training - Sponsor, CRA, & Site Collaboration". The third advertisement is titled "Treat Jock Itch" and includes the URL "www.Canesten.com.au/Jock-Itch" and the text "Find Relief With Canesten® Cream, Australia's Most Trusted Treatment".

Drug Information Online
Drugs.com

enter a search term

Browse all medications: A B C D E F G H I J K L M N O P Q R S T U V W X Y Z Advanced Search

Home > News > Clinical Trials

Print Save or Share

Sign In or Register

username

DURECT Reports Data From European Phase IIb Shoulder Study of Posidur) (SABER-Bupivacaine) and Amendment of the Nycomed Agreement

Ads by Google

[55/YO Mum Looks 35](#)
www.CollagenRenew.net/Anti_Wrinkles Mum Reveals Shocking Trick for Erasing Wrinkles! Doctors Hate Her

[Trifecta Multimedical](#)
www.TrifectaMultimedical.com Online Investigator Training - Sponsor, CRA, & Site Collaboration

[Treat Jock Itch](#)
www.Canesten.com.au/Jock-Itch Find Relief With Canesten® Cream, Australia's Most Trusted Treatment

Surgical site injection shoulder surgery

.... a statistically significant reduction in pain intensity versus SABER-Placebo.

.....indicated a clear clinically relevant trend in opioid sparing for POSIDUR compared to SABER-placebo



Block quality

Unintended sequelae of prolonged block

Effect on tissues and healing

Slow release opioid

Obstetric Anesthesiology
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Single-Dose, Extended-Release Epidural Morphine (DepoDur™) Compared to Conventional Epidural Morphine for Post-Cesarean Pain

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BACKGROUND: A single-dose of neuraxial morphine sulfate provides good post-Cesarean analgesia; however, its efficacy is limited to the first postoperative day. In a recent phase III study, extended-release epidural morphine (EREM) formulation provided more effective, prolonged analgesia after Cesarean delivery, compared to conventional epidural morphine. However, the study protocol did not allow for the use of nonsteroidal antiinflammatory drugs, used various postoperative analgesics, and monitoring and treatment of respiratory depression were not standardized. Our aims in this study were to compare postoperative analgesic consumption, pain scores and side effects of EREM with conventional morphine for the management of post-Cesarean pain in a setting more reflective of current obstetric practice.

METHODS: Seventy healthy parturients undergoing elective Cesarean delivery were enrolled in this randomized, double-blind study. Using a combined spinal epidural technique, patients received an intrathecal injection of bupivacaine 12 mg and fentanyl 10 mcg. After closure of the fascia, a single-dose of either conventional morphine 4 mg or EREM 10 mg was administered epidurally. Postoperatively, all

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Lessons Learned with Extended-release Epidural Morphine after Total Hip Arthroplasty

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Meta-analysis of the effect of extended-release epidural morphine versus intravenous patient-controlled analgesia on respiratory depression

.... EREM was associated with significantly higher odds of respiratory depression compared to IV-PCA (odds ratio = 5.74).....;

Anesthesia for the 21st century

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- ✓ **improved convenience**
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New horizons

New drugs are expensive to make – circa \$1 billion

Technology for delivery devices is clever, and growing rapidly

The role, and the genuine benefit, must be carefully examined

Monitoring of analgesia, looks like an exciting opportunity