New Methods for Analgesia Delivery

Guy Ludbrook MBBS  PhD  FANZCA

Royal Adelaide Hospital and University of Adelaide
South Australia
“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

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

- 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
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
“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 Remifentanil in Vascular Patients Improves Hemodynamics and Decreases Remifentanil Requirement

<table>
<thead>
<tr>
<th>Table 2. Hemodynamic Events</th>
<th>Group I, RIVA</th>
<th>Group II, TCIR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least 1 intraoperative episode</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>16</td>
<td>6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>2</td>
<td>0.08</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>1</td>
<td>0.16</td>
</tr>
<tr>
<td>Patients receiving intraoperatively</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ephedrine</td>
<td>19</td>
<td>19</td>
<td>0.50</td>
</tr>
<tr>
<td>Neosynephrine</td>
<td>13</td>
<td>10</td>
<td>0.19</td>
</tr>
<tr>
<td>Patients receiving during recovery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicardipine administration</td>
<td>14</td>
<td>9</td>
<td>0.07</td>
</tr>
<tr>
<td>B-Blockers administration</td>
<td>16</td>
<td>10</td>
<td>0.04</td>
</tr>
<tr>
<td>Need for morphine titration</td>
<td>4</td>
<td>3</td>
<td>0.34</td>
</tr>
</tbody>
</table>

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

De Castro et al., Anaesth Analg 96:33-38, 2003
.... a lower incidence in apnea and respiratory depression (TCI $n = 7$, MCI $n = 16$, $P < 0.05$) …
Anesthesia for the 21st century

Theodore H. Stanley, MD

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

- 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
Intraoperative measurement of analgesia

Pupillometry
Response indices
  EMG
  EEG
Heart rate/plethysmography
Pupillometry
“…. 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

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

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

Sabourdin N et al. A282 Anesthesiology 2011, Chicago IL
Comparison of Surgical Stress Index-guided analgesia with standard clinical practice during routine general anaesthesia

Xinzhong Chen et al.

### Unwanted events

<table>
<thead>
<tr>
<th></th>
<th>SSI-guided</th>
<th>Standard practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>hypertension</td>
<td>11*</td>
<td>84</td>
</tr>
<tr>
<td>hypotension</td>
<td>5*</td>
<td>67</td>
</tr>
<tr>
<td>tachycardia</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>bradycardia</td>
<td>23*</td>
<td>111</td>
</tr>
<tr>
<td>movements</td>
<td>3*</td>
<td>14</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>42</strong>*</td>
<td><strong>278</strong></td>
</tr>
</tbody>
</table>

Chen et al., Anesthesiology 112:1175-83, 2010
Intravenous drug administration
Matching the drug to the clinical need
Use of Remifentanil 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 remifentanil with intramuscular pethidine for labour analgesia

Anaesthesia 66(9) 796-801, 2011
Intravenous drug combinations
pain protocol in PACU

<table>
<thead>
<tr>
<th></th>
<th>AM group</th>
<th>M group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to comfort (min)</td>
<td>32.8 ± 26</td>
<td>40.9 ± 34</td>
</tr>
<tr>
<td>Volume to achieve comfort (ml)</td>
<td>15 ± 17</td>
<td>15.2 ± 11</td>
</tr>
<tr>
<td>Time to discharge (min)</td>
<td>88.4 ± 55</td>
<td>105.3 ± 75</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± S.D.

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

Alkhazrajy et al., Acute Pain 9, 13-19, 2007
Intravenous drug combinations
patient controlled analgesia

Addition of remifentanil 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 remifentanil 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
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
¹Sir Charles Gairdner Hospital, Perth, WA, Australia, ²Fremantle Hospital, Perth, WA, Australia

✓ Lower pain scores
✓ Less likely to need ketamine supplementation
✓ Unchanged sleep disturbance
Anesthesia for the 21st century

Theodore H. Stanley, MD

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

- 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
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.

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

Pharmacokinetic analysis
i.v. versus nasal

Delayed time to Cmax (13 vs 6 min)

Lower Cmax (1.2 vs 2.0 ng/mL)

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

Foster et al., Ann Pharmacother 42(10):1380-7, 2008
Anesthesia for the 21st century

Theodore H. Stanley, MD

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

- 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
Transdermal delivery

- No needles
- Sustained release
- Tough challenge - skin is there for a reason
Technologies

- Iontophoresis
- Nanotechnology
- Other
Iontophoresis

Reducing drug particle size to enhance drug dissolution

iCeutica’s proprietary SoluMatrix reformulation platform is a straightforward, scaleable 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 dry milling methodology which both mills the drug particles into a more fine and uniform form.
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

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

<table>
<thead>
<tr>
<th></th>
<th>PCA</th>
<th>ITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ease of use - patients</td>
<td>4.18</td>
<td>4.47</td>
</tr>
<tr>
<td>(higher is better)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ease of use - nurses</td>
<td>1.09</td>
<td>0.47</td>
</tr>
<tr>
<td>(lower is better)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Mean fentanyl plasma concentrations versus time after iontophoresis performed for 1 h (0.17 mA/cm² direct current) in rat. Fentanyl (40 µg/mL) was introduced in a citrate buffer pH 5 (0.01 M) (n = 9).
Spray on fentanyl

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

Sub-category:
Supportive Care

Category:
Patient and Survivor Care

Meeting:
2005 ASCO Annual Meeting

Session Type and 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:

Author(s):
Anesthesia for the 21st century

Theodore H. Stanley, MD

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

- 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
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
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 Australia1, SkyePharma Inc. San Diego CA USA2, SkyePharma Inc. San Diego CA USA3, SkyePharma Inc. San Diego CA USA4

Figure 1: Mean (SD) Bupivacaine Plasma Concentrations

- **Marcain® 50 mg**
- **SKY0402 100 mg**
- **SKY0402 175 mg**

**Plasma Bupivacaine Concentration (ng/ml)**

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

Haemorrhoids

Clinical Anesthesiology

Bupivacaine Formulation Extends Local Relief

by Dave Levan

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.
A SINGLE ADMINISTRATION OF DEPONBUPIVACAI® INTRAOPERATIVELY RESULTS IN PROLONGED DETECTABLE PLASMA BUPIVACAI AND ANALGESIA IN PATIENTS UNDERGOING INGUINAL HERNIA REPAIR

Richard M. Longford, FRCA; G.M. Chappell, FRACS; Jeff A. Karrasch, FRAG

Pain and Anaesthesia Research Centre, St. Bartholomew's Hospital, London, UK; Department of Surgery, Rockville Hospital, Rockville, Australia; Australian Clinical Research Organisation, Brisbane, Australia

ABSTRACT

Purpose: To determine if a single intraoperative dose of Depobupivacaine® (20 mg) was sufficient to provide postoperative analgesia in patients undergoing inguinal hernia repair.

Methods: A double-blind, randomized, placebo-controlled, parallel group study was conducted in a tertiary hospital setting. Patients undergoing inguinal hernia repair were randomized to receive either Depobupivacaine® (20 mg) or saline placebo. Blood samples were taken preoperatively and at 2, 4, 6, 8, 10, and 12 hours postsurgery. Plasma concentrations of bupivacaine were measured using high-performance liquid chromatography.

Results: Depobupivacaine® significantly enhanced plasma concentrations of bupivacaine compared to placebo at all time points. The effect was sustained for up to 12 hours postoperatively. No adverse effects were reported.

CONCLUSIONS

Depobupivacaine® provides prolonged analgesia in patients undergoing inguinal hernia repair.

INTRODUCTION

The use of local anesthetics for surgical procedures has been shown to reduce postoperative pain and analgesic requirements. Depobupivacaine® is a long-acting local anesthetic formulation that may provide prolonged analgesia.

METHODS

Patients undergoing inguinal hernia repair were randomized to receive either Depobupivacaine® (20 mg) or saline placebo. Blood samples were taken preoperatively and at 2, 4, 6, 8, 10, and 12 hours postsurgery. Plasma concentrations of bupivacaine were measured using high-performance liquid chromatography.

RESULTS

Depobupivacaine® significantly enhanced plasma concentrations of bupivacaine compared to placebo at all time points. The effect was sustained for up to 12 hours postoperatively. No adverse effects were reported.

CONCLUSIONS

Depobupivacaine® provides prolonged analgesia in patients undergoing inguinal hernia repair.

REFERENCES

Shoulder repair

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

Theodore H. Stanley, MD

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

- 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
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