Postoperative Analgesia: Transdermal

Klaus A. Lehmann
Department of Anaesthesiology
University of Cologne, Germany

Inefficacy of high-dose transdermal fentanyl in a patient with neuropathic pain, a case report.

Transdermal fentanyl for the treatment of pain after major urological operations

Patient, after admittance, with a total of 34 fentanyl TTS patches of 100 μg/h located on the anterior and posterior body surface.

References (1): Recent Publications
• Glerum LE et al.; Analgesic effect of the transdermal fentanyl patch during and after caesarian section. Vet Surg 2001;30:33
Transdermal Fentanyl

The PCA-Principle:

WYNIWYG
What you need is what you get.

Opioids: Transdermal Application

Passive
- Dihydroetorphine
- Buprenorphine
- Fentanyl
- Morphine (de-epithelialised skin)

Active
- Buprenorphine
- Fentanyl
- Hydromorphone
- Nalbuphine
- Morphine
- Sufentanil

Partial versus full agonists for opioid-mediated analgesia – focus on fentanyl and buprenorphine


Rat paw withdrawal after low and high thermal stimulation (ED50 in µg/kg)

<table>
<thead>
<tr>
<th></th>
<th>Low intensity ED50</th>
<th>High intensity ED50</th>
<th>Ratio high / low ED50</th>
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<tbody>
<tr>
<td>Fentanyl</td>
<td>15</td>
<td>32</td>
<td>2.3</td>
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<tr>
<td>Buprenorphine</td>
<td>16</td>
<td>152</td>
<td>24</td>
</tr>
<tr>
<td>Morphine</td>
<td>360</td>
<td>2200</td>
<td>11.8</td>
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Postop. pain control by transdermal fentanyl. Comparison of two dosages to a fixed-interval i.m. morphine regimen …

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Opioid-mediated analgesia


Rat paw withdrawal

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Postop. pain control by transdermal fentanyl. Comparison of two dosages to a fixed-interval i.m. morphine regimen …
Continuous administration of fentanyl for postoperative pain: epidural, intravenous and transdermal routes …

54 patients, 75 µg/h fentanyl by 3 routes at constant rate provided almost equal amount of analgesia, but continuous epidural application impaired spontaneous respiration.

Transdermal fentanyl after abdominal hysterectomy …
Sandler et al.; Anesthesiology 81:1169 (1994)

Transdermal fentanyl 50 or 75 µg/h, applied 2 h before surgery to 120 women. Between 5 and 36 h, the TTSF groups had significantly increased abnormal respiratory pattern including apneic episodes.

Postoperative analgesia and plasma levels after transdermal fentanyl for orthopedic surgery …

40 adult patients with transdermal fentanyl 75 µg/h or placebo, 72 h observation period. Additional morphine use was significantly lower in the active group. Plasma fentanyl concentrations were in the normal range (1.63 ng/ml).

Postoperative analgesia with transdermal fentanyl following lower abdominal surgery
Broome et al.; Anesthesia 50:300 (1995)

81 hysterectomy patients with transdermal fentanyl 25, 50 or 75 µg/h vs. placebo. Overall sedation scores were not increased by transdermal fentanyl, but respiratory rates decreased with higher dosage.

Biopharmaceutics of a new transdermal fentanyl device

Of the 14 male surgical subjects who received postop. transdermal fentanyl (Cygnus device), 3 had clinically significant toxicity, mandating early removal of the device.

Transdermal fentanyl 50 or 75 µg/h appeared to have some advantages over the currently available Duragesic transdermal device, which is contraindicated for postoperative pain.

Concerns exist regarding the side effects of this new transdermal fentanyl patch.

Postoperative pain control with a new transdermal fentanyl delivery system
Miguel et al; Anesthesiology 83:470 (1995)

143 gynecological patients with postop. placebo or fast onset Anaquest transdermal fentanyl 60-80 or 90-100 µg/h + M-PCA

The variability in effect of the Cygnus transdermal fentanyl device is appreciably greater than that reported for the currently available Duragesic transdermal device, which is contraindicated for postoperative pain.
Pharmacokinetics of transdermal fentanyl in the peri-operative period in young children
Paul et al., Anaesthesia 55:1202 (2000)

Time course of fentanyl concentrations up to 144 h after application (8 children 18-60 months, single dose 25 µg/h for 72 h)

Does continuous delivery of transdermal fentanyl affect analgesic efficacy or patient safety?

Cumulative opioid requirements (TTS fentanyl + PCA morphine equivalents)

No significant advantage to the routine use of continuous transdermal opioid delivery in patients receiving iv PCA

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Transdermal fentanyl system plus im ketorolac for the treatment of postoperative pain

Transdermal fentanyl 70-80 µg/h vs. placebo in 92 patients. The active group required less rescue ketorolac, but showed slightly more oxygen desaturation.

VAS following TTS Fentanyl in 62 orthopedic patients receiving 50 or 75 µg/h or placebo 2 h before induction + morphine PCA

No significant differences

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Transdermal fentanyl in postoperative pain

• 40 ASA I-II patients, 18-69 yr, abdominal surgery
• transdermal fentanyl 50-75 µg/h, applied 60 min prior to induction, vs. placebo
• less 36 h postoperative ketorolac or morphine requirements with active treatment
• no clinically relevant respiratory depression reported

Average fentanyl plasma concentrations at 12 and 24 h: 0.98 and 1.22 ng/ml

Recruitment was stopped after enrolment of 24 patients, on safety grounds.


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Average pulse oximeter readings & mean time with saturation below 90%; ASA I patients undergoing upper abdominal surgery, receiving 100 µg/h fentanyl or placebo.


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Perioperative pharmacokinetics of transdermal fentanyl in elderly and young adult patients

Mean (SEM) plasma fentanyl concentrations in 9 elderly (64-82 yr) and 10 young (25-38 yr) adult patients; TTSF 50 μg/h, 72 h application

No difference in postop. PCA morphine requirements between groups; 2 cases of respiratory depression after 16 and 26 h; transdermal fentanyl not recommended for postoperative use

Active Transdermal Application

- Iontophoresis
- Electrophoresis (Electroosmotic Transport)
- Electroporation (high voltage electric field pulses)
- Phonophoresis, Sonophoresis (Ultrasound)

Iontophoresis: an alternative to the use of carriers in cutaneous drug delivery

Iontophoretic pathways:
- a) appendageal
- b) intercellular

Iontophoresis: Clinical Application
antibiotics
glucocorticoids, antihistaminics
peptides
local anaesthetics
  - lidocaine, mepivacaine, procaine
  - NSAIDs
  - diclofenac, ketoprofen, ketorolac, salicylic acid..
  - opioids
  - hydromorphone, fentanyl, morphine, sufentanil

Dermal anaesthesia: comparison of EMLA cream with iontophoretic local anaesthesia
The iontophoresis of fentanyl citrate in humans

Mean ± SEM fentanyl concentration vs. time after 120 min iontophoretic fentanyl delivery in different currents (5 adult volunteers)

Fentanyl delivery from an electrotransport system

E-TRANS: continuous delivery with 100 µA for 26 h, additional boluses at t = 1 or t = 25 h

Electrically-assisted transdermal delivery of buprenorphine
Bose et al.; J Control Release 73:197 (2001)

Effect of iontophoresis for 4 h (0.5 mA/cm²) and electroporation (500 V, 10 ms, 20 pulses) followed by passive delivery for 24 h through human epidermis

References (2): Other Drugs
- Hagihara R et al.: A case of effective treatment with clonidine ointment for herpetic neuralgia after bone marrow transplantation in a child. Masui 2002;51:777

References (3): Nitroglycerine
- Lauretti GR et al.: Transdermal nitroglycerine enhances spinal neostigmine postoperative analgesia following gynecological surgery. Anesthesiology 2000;93:943
- Lauretti GR et al.: Transdermal nitroglycerine enhances spinal sufentanil postoperative analgesia following orthopedic surgery. Anesthesiology 1999;90:734

References (4): Mishaps
- Alshaf M, Stockwell M: Respiratory failure due to the combined effects of transdermal fentanyl and epidural bupivacaine/diamorphine following radical nephrectomy. J Pain Symptom Manage 2000;20:218
- Hardwick WE et al.: Respiratory depression in a child unintentionally exposed to transdermal fentanyl patch. South Med J 1997;90:962
Transdermal postoperative analgesia.

In vivo iontophoresis of fentanyl and sufentanil in rats … Thysman, Préat; Anesth Analg 77:67 (1993)

- Nevertheless, a major drawback of the transdermal administration, both by iontophoresis or passive diffusion, of a lipophilic compound such as fentanyl or sufentanil is drug accumulation in the skin and its slow release from the cutaneous depot.
- The delivery of the drug could be sustained for several hours after current cutting and/or patch withdrawal.

Transdermal fentanyl citrate … effects on postoperative pulmonary function Mason HH; Am J Crit Care 2:61 (1993)

Current postoperative analgesic therapies that include concomitant use of narcotic agonists and nonsteroidal anti-inflammatory drugs require adjustment of drug dosages to provide adequate pain relief while avoiding drug-induced complications.