Revival of intravenous lidocaine for pain treatment

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Pharmacology of Lidocaine

- amino-amide, sodium channel blocker
- Plasma $\frac{1}{2}$ Life – 8 minutes
- Metabolism:
  - Hepatic: 90% of clearance
    - rapid; cytochrome P450 1A2
  - Renal - 10% clearance; renal dysfunction - metabolites accumulation
  - Metabolites
    - monoethylglycinexylidide (MEGX) $\frac{1}{2}$ life 2 hours
    - glycinexylidide (GX) – $\frac{1}{2}$ life 10 hours
      - 1/10 convulsive potency
Pharmacology of Lidocaine

Dose and Toxicity

- **Steady State**
  - Bolus 1-1.5 mg/kg
  - Infusion >1.0 mg/kg/h

- **Lightheadedness** - 5 mg/L
- **Unconsciousness** - 10 mg/L
- **Seizures** - (12-18) mg/L
- **Respiratory and Cardiac Depression** - (20-24) mg/L
Effect of Intravenous Lidocaine on Volatile Anesthetic Requirements

- Prospective cohort study, no controls
- 20 ASA I & II patients
  - “variety of surgeries involving incision of skin of trunk”
- Constant infusion Lidocaine 3-6 mg/kg/h
- N₂O/halothane
- Venous plasma levels just before incision
  - Observed movement of patients under IV lidocaine/N₂O /halothane
  - Correlate to blood levels of lidocaine

Himes et al.
Anesthesiology 1977;47:437,
Effect of Intravenous Lidocaine on Volatile Anesthetic Requirements

Conclusion: lidocaine blood levels of 3.5 mg/L = 0.1 MAC halothane
Effect of Intravenous Lidocaine on Volatile Anesthetic Requirements

- Non randomized
- no controls
- small number of subjects

- One of the first studies to document MAC reducing effect of lidocaine
- MAC of halothane reduced by 10-45% between plasma levels of (3.5-11.6) mg/L

Himes et al. Anesthesiology 1977;47:437,
Protocol: 5 patients with clinical neurologic pain undergoing experimental induced ischemic pain (tourniquet). They received a lidocaine bolus of 3mg.kg$^{-1}$ followed by an infusion of 4mg.min$^{-1}$

Boas et al.
Brit J Anaesth 1982;54:501,
Analgesic response to intravenous lidocaine in the treatment of neuropathic pain

- Prospective cohort study, no controls
  - 13 patients studied
    - 10 peripheral neuropathic pain
    - 3 central neuropathic pain
  - Baseline pain assessment
  - Liver and renal disease excluded

- Lidocaine 500mg i.v over 60 minutes (8.35 mg/min IV)
  - pain scores and venous lidocaine levels every 10 minutes
  - correlate ED50, ED90 to lidocaine blood concentrations

Ferrante et al. Anesth Analg 1996;82:91,
## Analgesic response to intravenous lidocaine in the treatment of neuropathic pain

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr): gender</th>
<th>Diagnosis</th>
<th>Complete analgesia?</th>
<th>Lidocaine dose for complete analgesia (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47:M</td>
<td>Central pain (spinal cord injury)</td>
<td>Yes</td>
<td>416.5</td>
</tr>
<tr>
<td>2</td>
<td>67:M</td>
<td>Burning dysesthesia (L5)</td>
<td>Yes</td>
<td>358.2</td>
</tr>
<tr>
<td>3</td>
<td>42:M</td>
<td>Saphenous neuropathy</td>
<td>No</td>
<td>&gt;500?</td>
</tr>
<tr>
<td>4</td>
<td>70:F</td>
<td>Burning dysesthesia (L5)</td>
<td>Yes</td>
<td>374.9</td>
</tr>
<tr>
<td>5</td>
<td>35:F</td>
<td>Diabetic polyradiculopathy</td>
<td>Yes</td>
<td>441.5</td>
</tr>
<tr>
<td>6</td>
<td>65:M</td>
<td>Intercostal neuralgia</td>
<td>Yes</td>
<td>399.8</td>
</tr>
<tr>
<td>7</td>
<td>66:M</td>
<td>Phantom foot pain</td>
<td>No</td>
<td>&gt;500?</td>
</tr>
<tr>
<td>8</td>
<td>32:F</td>
<td>Central pain (Dejerine-Roussy syndrome)</td>
<td>Yes</td>
<td>416.5</td>
</tr>
<tr>
<td>9</td>
<td>52:M</td>
<td>Sympathetically maintained pain</td>
<td>No</td>
<td>&gt;500?</td>
</tr>
<tr>
<td>10</td>
<td>30:F</td>
<td>Diabetic neuropathy</td>
<td>Yes</td>
<td>333.2</td>
</tr>
<tr>
<td>11</td>
<td>48:M</td>
<td>Sympathetically maintained pain</td>
<td>Yes</td>
<td>408.2</td>
</tr>
<tr>
<td>12</td>
<td>39:F</td>
<td>Diabetic radiculopathy</td>
<td>Yes</td>
<td>408.2</td>
</tr>
<tr>
<td>13</td>
<td>57:F</td>
<td>Meralgia paresthetica</td>
<td>Yes</td>
<td>191.6</td>
</tr>
</tbody>
</table>

Ferrante et al.  
Anesth Analg 1996;82:91,
Analgesic response to intravenous lidocaine in the treatment of neuropathic pain

- 10 patients complete relief, 3 patients partial relief
- Complete relief in 8/11 peripheral pain and 2/2 central pain
- Time to onset of complete analgesia 45 +/- 8.6 min
- ED20 330mg; ED50 372 mg; ED90 416 mg
- Serum concentrations for complete analgesia 3.8 +/- 1.0 mg/L

Ferrante et al. Anesth Analg 1996;82:91,
Protocol: n = 32. RCT, crossover trial

**Stump Pain**

**Phantom Pain**

**Self-reported outcomes**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Stump Pain Relief</th>
<th>Phantom Pain Relief</th>
<th>Satisfaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>32.8 ± 33.6 *</td>
<td>25.8 ± 31.2</td>
<td>39.3 ± 37.6 *</td>
</tr>
<tr>
<td>Morphine</td>
<td>44.8 ± 35.4 *</td>
<td>47.9 ± 38.2 *</td>
<td>45.9 ± 35.5 *</td>
</tr>
<tr>
<td>Placebo</td>
<td>8.2 ± 15.9</td>
<td>3.2 ± 10.1</td>
<td>9.8 ± 21.0</td>
</tr>
</tbody>
</table>

Stump pain – phantom pain have different mechanisms

Martin et al. Anesthesiology 2008;109:118,
Mechanism of action as systemic analgesic

• Central anti-hyperalgesic and anti-allodynic
  – Evidence of central action at postero-lateral thalamus
  – Action at dorsal horn

• At peripheral A-delta and C fibre mechanical and chemical nociceptors
  – Higher selectivity for injured nerve fibers
  – Tissue injury - major input from chemo-receptors to CNS
    • Mechano-insensitive nociceptors
    • sensitive to small dose of lidocaine
    • prevent central hyperalgesia and improve postop pain

Koppert et al
Pain 2000;85:217,
Lidocaine plasma concentrations:
2.4±0.6 mg/L at the end of surgery
2.7±1.1 mg/L after 24h
Intravenous Lidocaine Infusion Facilitates Acute Rehabilitation after Laparoscopic Colectomy

Abdourahamane Kaba, M.D.,* Stanislas R. Laurent, M.D.,† Bernard J. Detroz, M.D.,† Daniel I. Sessler, M.D.,‡ Marcel E. Durieux, M.D., Ph.D.,§ Maurice L. Lamy, M.D.,∥ Jean L. Joris, M.D., Ph.D.#

- endocrine and metabolic responses were similar in the 2 groups

Possible mechanisms:
- reduction in opioid consumption
- antiinflammatory properties of lidocaine
- direct inhibition of the sympathetic
- myenteric plexus?
Systemic Lidocaine Shortens Length of Hospital Stay After Colorectal Surgery

- Systemic lidocaine significantly ↓ IL-6, IL-8, C3a and expression of P-selectin
- Systemic lidocaine reduces hospital stay by 1 day
- Lidocaine blood levels 1.1 - 4.2 mg/L

Bolus (1.5mg/kg of lidocaine before induction, followed by an infusion 2mg/min) until 4h postop

Herroeder et al
Ann Surg 2007;246:192,
Intraoperative intravenous lidocaine reduces hospital length of stay following open gastrectomy for stomach cancer in men☆

Protocol: n = 48 RCT. Lidocaine 1.5 mg.kg⁻¹ 20min before surgery followed by 1.5mg.kg⁻¹.h⁻¹ until end of the procedure

Prevention of central hyperalgesia?

Kang et al. J Clin Anesth 2012;24:465,
Continuous intravenous lidocaine in the treatment of paralytic ileus due to severe spinal cord injury

7 patients with complete paralytic spinal cord injury-related ileus resistant to neostigmine

Successful treatment by i.v. lidocaine infusion bolus 1mg/kg, infusion 2-3 mg/min in 5 patients

Lidocaine effectiveness may primarily stem from its anti-inflammatory properties and reduced opioid requirements

Beneficial effects on imbalance due to excessive parasympathetic suppression and/or sympathetic stimulation of the colon (?)
Intravenous Lidocaine Is as Effective as Epidural Bupivacaine in Reducing Ileus Duration, Hospital Stay, and Pain After Open Colon Resection

- Open colon surgery
- Prospective, randomized
- 22 patients EDA (bupivacaine 0.125% & hydromorphone 6µg/ml) vs. 20 patients IV lidocaine 1-2mg/min
- **No difference** in bowel function, pain, hospital length of stay

→ IV infusion of local anesthetic is an effective **alternative** to epidural therapy

<table>
<thead>
<tr>
<th>Measures of Return of Bowel Function,† d</th>
<th>Epidural (n = 20)</th>
<th>IV Lidocaine (n = 22)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first flatus</td>
<td>1.6 (1.2–34)†</td>
<td>2.7 (1.9–3.5)</td>
<td>0.17</td>
</tr>
<tr>
<td>Time to first bowel movement</td>
<td>3.0 (1.7–4.5)</td>
<td>2.9 (2.3–3.6)</td>
<td>0.99</td>
</tr>
<tr>
<td>Time of advancement to clear liquid diet‡</td>
<td>3.6 (2.6–4.8)</td>
<td>2.9 (2.7–3.7)</td>
<td>0.47</td>
</tr>
<tr>
<td>Inpatient time§</td>
<td>5.3 (4.7–7.9)</td>
<td>5.1 (4.8–5.9)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Svenson et al. RAPM 2010; 35:370,
• Multiple sites within the CW5 are activated by colorectal distension (CRD)

• Two spinal neuronal populations encode for CRD in an excitatory, graded fashion and can be distinguished from each other

Ness, T.J.
Anesthesiology 2012;92:1685,
Perioperative Intravenous Lidocaine Decreases the Incidence of Persistent Pain After Breast Surgery

Protocol: n = 36 RCT, double-blind
Before surgery bolus 1.5mg.kg⁻¹ followed by an infusion of 1.5mg.kg⁻¹.h⁻¹ until 1h after skin closure

Central sensitization could explain chronic pain

Postoperative morphine consumption

<table>
<thead>
<tr>
<th></th>
<th>Lidocaine Group (n = 17)</th>
<th>Control Group (n = 19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia request in 24h</td>
<td>13/17 (76.5%)</td>
<td>14/19 (73.3%)</td>
<td>0.849</td>
</tr>
<tr>
<td>Morphine 2h</td>
<td>2.6 (+ 2.5)</td>
<td>3.0 (+ 3.8)</td>
<td>0.869</td>
</tr>
<tr>
<td>Morphine 4h</td>
<td>0.5 (+ 1.3)</td>
<td>1.4 (+ 2.3)</td>
<td>0.179</td>
</tr>
<tr>
<td>Morphine 24h</td>
<td>2.1 (+ 5.1)</td>
<td>4.2 (+ 10.3)</td>
<td>0.623</td>
</tr>
<tr>
<td>Morphine 2d</td>
<td>0.3 (+ 1.2)</td>
<td>3.1 (+ 8.7)</td>
<td>0.310</td>
</tr>
<tr>
<td>Morphine 3d</td>
<td>0.2 (+ 0.7)</td>
<td>2.3 (+ 5.7)</td>
<td>0.310</td>
</tr>
<tr>
<td>Morphine 4d</td>
<td>0</td>
<td>0.5 (+ 2.3)</td>
<td>0.344</td>
</tr>
<tr>
<td>Morphine 5d</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Morphine 6d</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Morphine 7d</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Chronic pain assessment (at 3mo follow-up)

<table>
<thead>
<tr>
<th></th>
<th>Lidocaine Group (n = 17)</th>
<th>Control Group (n = 19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPSP</td>
<td>2 (11.8%)</td>
<td>9 (47.4%)</td>
<td>0.031*</td>
</tr>
<tr>
<td>S-PRI</td>
<td>1.1 (+ 3.9)</td>
<td>1.4 (+ 3.2)</td>
<td>0.049*</td>
</tr>
<tr>
<td>A-PRI</td>
<td>0.1 (+ 0.5)</td>
<td>0.7 (+ 2.1)</td>
<td>0.196</td>
</tr>
<tr>
<td>T-PRI</td>
<td>1.2 (+ 4.4)</td>
<td>2.1 (+ 5.3)</td>
<td>0.039*</td>
</tr>
<tr>
<td>PPI-VAS</td>
<td>2.6 (+ 7.5)</td>
<td>14.6 (+ 22.5)</td>
<td>0.025*</td>
</tr>
<tr>
<td>Overall pain intensity</td>
<td>0.2 (+ 0.5)</td>
<td>0.9 (+ 1.4)</td>
<td>0.023*</td>
</tr>
<tr>
<td>Interference with activities</td>
<td>1 (5.9%)</td>
<td>5 (10.5%)</td>
<td>0.182</td>
</tr>
<tr>
<td>Hypersensitivity (cm)</td>
<td>0.2 (+ 0.8)</td>
<td>3.2 (+ 4.5)</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

Grigoras et al.
Clin J Pain 2012;28:567,
Systemic administration of lidocaine reduces morphine requirements and postoperative pain of patients undergoing thoracic surgery after propofol–remifentanil-based anaesthesia

Protocol:  n = 40   Propofol - remifentanil – lidocaine 2 mg.kg\(^{-1}\).h\(^{-1}\)

- Significant \(\downarrow\) in morphine consumption in PACU
- Significant \(\downarrow\) VAS within the first 6 postop hours

Cui et al.  
Eur J Anaesthesiol 2010;27:41,
IV Lidocaine for transabdominal hysterectomy

Protocol: n = 65 RCT. Lidocaine 2 mg.kg-1.h-1 given 20 min before surgery until end of procedure


<table>
<thead>
<tr>
<th>Postoperative time (h)</th>
<th>Sal + PCEA at rest</th>
<th>Lidoc + PCEA at rest</th>
<th>Sal + PCEA coughing</th>
<th>Lidoc + PCEA coughing</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>4.53 ± 0.22</td>
<td>4.0 ± 0.11 P = 0.0293</td>
<td>6.13 ± 0.14</td>
<td>5.3 ± 0.14 P = 0.0031</td>
</tr>
<tr>
<td>8</td>
<td>4.27 ± 0.18</td>
<td>3.7 ± 0.10 P = 0.0111</td>
<td>5.37 ± 0.14</td>
<td>5.0 ± 0.10 P = 0.0484</td>
</tr>
<tr>
<td>12</td>
<td>3.70 ± 0.19</td>
<td>3.4 ± 0.10</td>
<td>4.97 ± 0.14</td>
<td>4.7 ± 0.11</td>
</tr>
<tr>
<td>24</td>
<td>3.13 ± 0.16</td>
<td>3.0 ± 0.15</td>
<td>4.3 ± 0.14</td>
<td>4.2 ± 0.10</td>
</tr>
<tr>
<td>48</td>
<td>2.70 ± 0.14</td>
<td>2.63 ± 0.11</td>
<td>3.67 ± 0.10</td>
<td>3.6 ± 0.09</td>
</tr>
<tr>
<td>72</td>
<td>1.90 ± 0.13</td>
<td>1.87 ± 0.10</td>
<td>2.83 ± 0.11</td>
<td>3.0 ± 0.10</td>
</tr>
</tbody>
</table>

PCEA = patient-controlled epidural analgesia; Sal = saline; Lidoc = lidocaine; VAS = visual analog scale.

Significant less pain at rest and during coughing
Protocol: \( n = 60 \). Lidocaine 1.5 mg.kg\(^{-1}\), then 1.5 mg.kg\(^{-1}\).h\(^{-1}\) 30 min before surgery until 1 h after end of surgery

Evolution of pressure pain threshold (kPa) determined with an algometer the day before surgery and at 24 and 48 h after surgery

Martin et al. Anesthesiology 2008;109:118,
Systemic Lidocaine as a Perioperative Analgesic

Method of administration

• Bolus 1-1.5mg/kg at (or before) induction
• Infusion 1.5 – 2.5 mg/kg/h
• Variety of procedures - bowel, orthopedics, ....
Systemic Lidocaine as a Perioperative Analgesic

Conclusions - pro

• small cohort and RCT studies
• 10% or greater volatile anesthetic sparing effect at a plasma level of 3.5 mg/L
• reduction in narcotic requirements at plasma levels between (1.9-3.7) mg/L
• improvement in pain scores postop
• quicker return of bowel function postop
• decreased length of stay of 1 day in one study
• analgesic effect through to POD 2-3
• toxicity not an issue at doses used
Systemic Lidocaine as a Perioperative Analgesic

Conclusions - con

- Study design lacking:
  - small
  - lack of power analysis
  - data collection imprecise (duration of infusion)
Effect of a sodium channel activator and blocker on the phosphorylation status of Src and ICAM-1 in NCI-H838 lung cancer cells

A i. pY419 Src
   total Src
Veratridine 0.015 [mM] - +

ii. pY512 ICAM-1
   total ICAM-1
Veratridine 0.015 [mM] - +

iii. Src
   ICAM-1
phospho / total
comparisons to control (1.0)
Veratridine 0.015 [mM] + +

B i. pY419 Src
   total Src
TNF 20 [ng/ml] - + + +
TTX 10^{-7} [M] - + + +

ii. pY512 ICAM-1
   total ICAM-1
TNF 20 [ng/ml] - + + +
TTX 10^{-7} [M] - + + +

iii. pY419 Src / total Src
   compared to control (1.1)
TNF 20 [ng/ml] + + + +
TTX 10^{-7} [M] + + + +

iv. pY512 ICAM-1 / total ICAM-1
   compared to control (1.1)
TNF 20 [ng/ml] + + + +
TTX 10^{-7} [M] + + + +

Piegeler et al.
Anesthesiology 2012;117:548,
Conclusion

LA have other effects than blocking NA+ channel. Clinical and experimental evidence have shown that their non-anesthetic effects are significant and have opened fascinating research fields.
Thank you for your attention