IV Lidocaine

- Introduction
- Acute pain
- Postoperative Ileus
- Inflammation
- Cancer Recurrence
- Pharmacokinetics and Toxicity
History

- 1943: synthesized by Nils Löfgren: “Xylocaine”. tested on his colleague Lundqvist
- Clinical research by T. Gordh
- 1949: first marketed as a topical anesthetic
- 1950: first report of IV use: antiarrhythmic
- 1954: de Clive-Lowe et al. *Anaesthesia*: “IV infusion of lidocaine during GA was shown to provide postoperative analgesia for more than 10 hours with low incidence of PONV”
- ‘60: Pain treatment in cancer, diabetic neuropathy, chronic pain
- ‘60: most widely used LA

IV Lidocaine - Introduction

2-diethylamine-N-(2,6-dimethylphenyl)-ethanamide

Hydrophobic

Hydrophilic
IV Lidocaine - Introduction

Mechanism of Action
- Blockade of voltage-gated Na+ channels => nerve conduction

Lower potency for K+ and Ca2+ channels (e.g. Ca2+ influx in DRG)

(Arias et al, 1999)

TRPV1-activation - Inhibition of glycine transporter 1 (GlyT1)
(Werdehausen et al, Anesthesiology 2012)

‘An anesthetic is not a special poison for the nervous system. It anesthetizes all the cells, benumbing all the tissues, and stopping temporarily their irritability.’

Claude Bernard, 1875, Leçons sur les anesthésiques et sur l’asphyxie

- Direct membrane interactions?
IV Lidocaine – Acute Pain

– Well established in treatment of
  • (pain associated with) burn injuries
    – Benlier 2012, Wasiak 2011 and 2012, Jonsson 1991, ...
  • Chronic neuropathic pain (cancer, diabetes)

– Effects in the perioperative setting not well understood:
  • MAC reduction up to 35%
  • Lower BIS values during TIVA for thoracic surgery?
    – Cui 2010
  • No effect on BIS and no correlation between BIS and [Lido]p
    – Hans 2010

=> Cortical suppression or pure antinociceptive effect?
Fig. 1. End-tidal concentration of sevoflurane in 40 patients during laparoscopic colectomy. Half of the patients received intravenous lidocaine (an intravenous bolus injection of 1.5 mg/kg lidocaine followed by a continuous infusion of 2 mg · kg\(^{-1}\) · h\(^{-1}\)); the other half received an equal volume of saline (saline). The sevoflurane concentration in the lidocaine group was significantly lower than in the placebo group (analysis of variance, \(P < 0.001\)). Data are presented as mean ± SEM. The differences between the two groups were statistically significant. \(P < 0.01\) at 15 and 30 min, and \(P < 0.001\) after 30 min.

Kaba, Anesthesiology 2007
IV Lidocaine – Acute Pain

Perioperative intravenous lidocaine infusion for postoperative pain control: a meta-analysis of randomized controlled trials

Perfusion intraveineuse périopératoire de lidocaïne pour le contrôle de la douleur postopératoire: une méta-analyse d’études randomisées contrôlées

Louise Vigneault, MD • Alexis F. Turgeon, MD • Dany Côté, MD • François Lauzier, MD • Ryan Zarychanski, MD • Lynne Moore, PhD • Lauralyn A. McIntyre, MD • Pierre C. Nicole, MD • Dean A. Fergusson, PhD
IV Lidocaine – Acute Pain

- Meta-analysis of 29 RCT’s, n= 1754
- Different kinds of surgery:
  - Abdominal (12), cardiac (3), thoracic (1), orthopedic (1), uro/gyn (5), other (2)
- Different types of control:
  - epidural (2), placebo/saline (24), morfine (1), mepiridine (1), no control (1)
- Different treatment regimens:
  - Loading dose, ctuous infusion, postop infusion
- Different outcome measures:
  - POP/opioid consumption, ileus, cardioprotection, neuroprotection, LOHS, time to extubation, QoR, immune response, neonatal outcome, uterine tone, SSR, inflammatory markers, ...
IV Lidocaine – Acute Pain

Results: POP at rest

- Significant reduction in POP at rest:
  - At 6 hrs: VAS score WMD -8.70 mm (n= 579, CI 95% -16.19 to -1.21)
  - At 12 hrs: VAS score WMD -6.52 mm (n = 398, CI 95% -12.12 to -0.91)

- No pain reduction beyond 12 hours postoperatively

Vigneault et al, Can J Anesth 2011
IV Lidocaine – Acute Pain

Results: POP during cough

- Significant reduction in POP during cough:
  - At 6 hrs: VAS score WMD -11.19 mm (n = 410, CI 95% -17.73 to -4.65)
  - At 12 hrs: VAS score WMD -7.44 mm (n = 280, CI 95% -14.24 to -0.63)
  - At 24 hrs: VAS score WMD -6.94 mm (n = 380, CI 95% -6.94 to -1.01)

- No pain reduction beyond 24 hours postoperatively

Vigneault et al, Can J Anesth 2011
IV Lidocaine – Acute Pain

Results: Reduction in postop morphine-equivalents

- MEQ calculated by authors as cumulative dose during ‘the postoperative period’
- Significant reduction in MEQ consumption:
  - WMD -8.4 mg MEQ (n = 690, CI 95%: -11.32 to -5.56 mg)

Vigneault et al, Can J Anesth 2011
IV Lidocaine – Acute Pain

Results: Sub-analysis for abdominal surgery

⇒ Effects of IV lidocaine on acute pain seem to be limited to abdominal surgery!

Vigneault et al, Can J Anesth 2011
IV Lidocaine – Acute Pain

Mechanism of pain relief: more than just Na+ channels...

- Peripheral effect:
  - Selective decrease in neuronal discharge of active peripheral fibres (A-delta and C are relatively sensitive to lidocaine)
  - Inhibition of GPCR- mechanism and other intracellular pathways (Hollmann 2000, Nagyl 1996)

- Central effect:
  - Central anti-hyperalgesic via NMDA receptor inhibition (Koppert 2000, Sugimoto 2003)
  - Inhibition of neurokinin receptor mediated pain transmission in spinal chord of rats (Nagyl 1996)
  
  => Selective decrease of pain transmission in spinal cord

- Anti-inflammatory effects (cfr infra)

... but yet to uncover
Conclusion:
- Good evidence for analgesic effect of IV lidocaine in abdominal surgery
- Less effective for other types of surgery
- Continuous infusion postoperatively
- Large differences in perioperative regimens
- Effect limited in time
- No toxic events reported
- CAVE publication bias!
IV Lidocaine – Acute Pain

Why is pain provoked by abdominal surgery particularly responsive to IV lidocaine??
IV Lidocaine – Bowel Function

Ileus post-abdominal surgery = a problem
IV Lidocaine – Bowel Function

- Ileus post-abdominal surgery = a problem
- Frequent reason for increased LOUS (= €)
- Pathogenesis multifactorial:
  - Abdominal pain
  - Opioid use
  - Sympathetic tone / SSR
  - GI hormonal disruption
  - Inflammation
- Evidence for lidocaine:

⇒ increased inhibitory neural input, heightened inflammatory responses, decreased propulsive movements and increased fluid absorption in the gastrointestinal tract.

Kurz, Drugs 2003
Risk Factors for Equine Postoperative Ileus and Effectiveness of Prophylactic Lidocaine

S. Torfs, C. Delesalle, J. Dewulf, L. Devisscher, and P. Deprez

Background: Postoperative ileus (POI) is a frequent and often fatal complication of colic surgery. Reliably effective treatments are not available.

Objectives: To determine risk factors and protective factors associated with POI, and to assess the effect of lidocaine IV on short-term survival.

Animals: One hundred and twenty-six horses that underwent small intestinal colic surgery and that survived for at least 24 hours postoperatively.

Methods: Retrospective cross-sectional study. The association of 31 pre-, intra-, and postoperative variables with POI and the association of lidocaine treatment with short-term survival were investigated. Associations were evaluated with univariable logistic regression models, followed by multivariable analysis.

Results: Significant associations of high heart rate (odds ratio [OR] = 1.05, 95% confidence interval [CI] 1.03–1.08), the presence of more than 8 L of reflux at admission (OR = 3.02, 95% CI 1.13–8.02) and the performance of a small intestinal resection (OR = 2.46, 95% CI 1.15–5.27) with an increased probability of POI were demonstrated. Prophylactic lidocaine treatment was significantly associated with a reduced incidence of POI (OR = 0.23, 95% CI 0.11–0.56). Lidocaine treatment was also significantly associated with enhanced short-term survival (OR = 0.30, 95% CI 0.09–0.98).

Conclusions and Clinical Importance: The variables associated with an increased risk of POI can be useful in identifying horses at risk of POI and in providing a more accurate prognosis. The results are supportive for lidocaine IV as an effective treatment after small intestinal colic surgery.

Keywords: Abdominal Fluid, Postoperative Ileus, Horses, Small Intestinal, Prophylactic Lidocaine.
IV Lidocaine – Bowel Function

Evidence in humans:

Meta-analysis

Meta-analysis of intravenous lidocaine and postoperative recovery after abdominal surgery

E. Marret¹, M. Rolin², M. Beaussier² and F. Bonnet¹

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Correspondence to: Dr E. Marret, Department of Anaesthesiology and Intensive Care, Hôpital Tenon, 4 Rue de la Chine, 75970 Paris Cedex 20, France (e-mail: emmanuel.marret@mn.ap-hop-paris.fr)

Marret et al 2008:
- Meta-analysis of 8 RCT’s
- Abdominal surgery: open, laparoscopic
- IV lidocaine versus Placebo
- N = 320, 161 patients, 159 controls
IV Lidocaine – Bowel Function

Objectives:
- Return of bowel function: 7/8
- LOHS: 5/8
- Postoperative pain (VAS): 7/8
- Postoperative opioid use: 5/8
- PONV: 3/8
- Inflammatory response: 3/8

Methods:
- Different regimens (loading dose, postop inf 0-24 hrs)
- Different procedures
- No epidurals

Marret et al, BJS 2008
**IV Lidocaine – Bowel Function**

Results: Return of bowel function: 7 RCT’s

<table>
<thead>
<tr>
<th>Reference</th>
<th>Lidocaine n</th>
<th>Ileus (h)*</th>
<th>Placebo n</th>
<th>Ileus (h)*</th>
<th>WMD (random)</th>
<th>Weight (%)</th>
<th>WMD (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herroeder et al.</td>
<td>31</td>
<td>66:60 (26:40)</td>
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<td>82:10 (33:80)</td>
<td>-15:50 (-30:92, -0:08)</td>
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<td>20</td>
<td>31:30 (11:50)</td>
<td>-13:30 (-19:73, -6:87)</td>
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<td>20</td>
<td>85:00 (20:76)</td>
<td>-6:00 (-16:81, 4:81)</td>
<td>10:07</td>
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</tr>
<tr>
<td>Wu et al.</td>
<td>25</td>
<td>22:10 (1:60)</td>
<td>25</td>
<td>22:90 (1:80)</td>
<td>-0:80 (-1:74, 0:14)</td>
<td>19:74</td>
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</tr>
<tr>
<td>Total</td>
<td>151</td>
<td></td>
<td>149</td>
<td></td>
<td>-8:36 (-13:24, -3:47)</td>
<td>100:00</td>
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</tr>
</tbody>
</table>

- Significant reduction in POI in 5/7 RCT’s
- Total WMD: -8.36 hours (95% CI -2.12 to -0.34 hrs, p = 0.007)

=> “Duration of POI was significantly diminished by continuous intravenous infusion of lidocaine”:

Marret et al, BJS 2008
IV Lidocaine – Bowel Function

Results: Return of bowel function:

Subgroup analysis:
- CCE (open and lap): WMD -1.23 hrs
- Colonic resection (open and lap): WMD – 12 hrs
- Laparoscopy: WMD -1.06 hrs
IV Lidocaine – Bowel Function

Results: Return of bowel function:

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<td>20</td>
<td>42:10 (16:00)</td>
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CAVE: Definition of return of bowel function not homogenous:
- Flatus
- Bowel movement
- Flatus and/or bowel movement
- Radiographic markers
- Solid meal

Marret et al, BJS 2008
IV Lidocaine – Bowel Function

Results: LOHS: 5 RCT's

- Significant reduction in LOHS in 3/5 RCT’s
- Total reduction: -0.84 days (95% CI -1.38 to -0.31 days, \( p = 0.002 \))

=> “Significant reduction in LOHS by continuous IV lidocaine (...) resulting from earlier recovery of bowel function”

Marret et al, BJS 2008
IV Lidocaine – Acute Pain

**Conclusion:**
- IV lidocaine during and after abdominal surgery:
  - Decreases incidence of POI
  - Decreases incidence of PONV
  - Reduces LOHS
  - Provides analgesia
- Most effective for major abdominal procedures
- Effect = large, low NNT
- Reduction in LOHS ⇔ epidural? CAVE!
IV Lidocaine – Bowel Function

Proposed mechanism?

Cir etiology of postoperative ileus:

- Abdominal pain
- Opioid use
- Sympathetic tone / SSR
- GI hormonal dysruption
- Inflammation
IV Lidocaine – Bowel Function

Proposed mechanism?

Abdominal pain:

- Colorectal Distension
- Inhibition of intestinal motility and propulsive activity
- Activation of visceral afferents
- Abdominal pain
- Spinal reflex arc
- Sympathetic hyperactivity

Liu 1995, Kuo 2006
IV Lidocaine – Bowel Function

Results: VAS: 6/8 RCT’s (abdominal surgery)

- Mild reduction in VAS (-5.93 mm)
- Reduction in (abdominal) pain // reduction in POI

Marret et al, BJS 2008
IV Lidocaine – Bowel Function

Proposed mechanism?

Cir etiology of postoperative ileus:

- Abdominal pain
- Opioid use
- Sympathetic tone / SSR
- GI hormonal dysruption
- Inflammation
IV Lidocaine – Bowel Function

Proposed mechanism?

Opioid use:
- Known effects on bowel function:
  - Mu receptor in GI tract
  - “Intravenous opioid therapy is significantly associated with POI and prolonged LOS” (Barletta, Ann Pharmacother 2011)
- Is it a pure opioid sparing effect?
  - IV LA => ↓ Per-operative as well as postoperative opioid use
IV Lidocaine – Bowel Function

Proposed mechanism?
Cir etiology of postoperative ileus:

- Abdominal pain
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IV Lidocaine – Bowel Function

Proposed mechanism?
Sympathetic tone

Colorectal Distension

Inhibition of intestinal motility and propulsive activity

Activation of visceral afferents

Abdominal pain

Spinal reflex arc

Surgery

Liu 1995, Kuo 2006
IV Lidocaine – Bowel Function

Proposed mechanism?

**Sympathetic tone:** Could lidocaine lower sympathetic tone and attenuate the surgical stress response (via epidural)?

**PRO:**
- Similar [lido]p seen after IV or epidural infusion (Inoue 1985, Shono 2003)

**CON:**
- [lido]p still very low compared to [] needed to obtain a local or regional nerve block: direct blockade of mesenteric plexus not likely
- No reduction in urinary catecholamines after lidocaine infusion (Kaba 2007)
IV Lidocaine – Bowel Function

Proposed mechanism?
Sympathetic tone, Kaba 2007

⇒IV lidocaine does NOT inhibit the SSR
- Blockade of nociception not profound enough?
- “... demonstrates that major benefits in postoperative recovery can be obtained without blocking the surgical stress response.”

Kaba et al, Anesthesiology 2007
IV Lidocaine – Bowel Function

Proposed mechanism?

Cfr etiology of postoperative ileus:

- Abdominal pain
- Opioid use
- Sympathetic tone / SSR
- GI hormonal dysruption
- Inflammation

“Yes, but our epidural takes care of all of these”
IV Lidocaine – Bowel Function

**Epidural analgesia**

**PRO**
- Better analgesia
- Less toxic [lido]p
- Patient-controlled

**CON**
- Up to 30% failure
- CI (anticoagulation)
- Side fx (hypotension, urinary retention, motoric blockade)
- Complications: haematoma, abscess

**IV lidocaine**

**PRO**
- Side fx profile
- Epidural inappropriate (laparoscopy)
- Few CI

**CON**
- Not as effective as epidural?
  (Swenson 2010)
- Concerns of toxicity
- Limited to abdominal surgery?
"(...) IV infusion of local anesthetic may be an effective alternative to epidural therapy in patients in whom epidural anesthesia is contraindicated or not desired"
Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery

C. P. Kuo¹, S. W. Jao², K. M. Chen³, C. S. Wong¹, C. C. Yeh¹, M. J. Sheen¹ and C. T. Wu¹*

In the present study, epidural or i.v. lidocaine before the start of surgical procedure provided significant pain relief with reduced pain intensity, diminished volatile agent and opioid consumption, accelerated return of the bowel function, and attenuated production of IL-6, IL-8 and IL-1RA. The benefit of lidocaine was more obvious in Group TEA.

-60 pts for colonic surgery randomized to TEA with Lidocaine / IV Lidocaine (and sham-TEA) / Placebo and sham-TEA
**IV Lidocaine – Inflammation**

- Surge of IL-6, IL-8 and IL-1RA after colonic surgery
- Cytokine levels significantly reduced by TEA > IV lido
- The lowest cytokine response was associated with the best bowel function

Kuo et al, BJA 2006
IV Lidocaine – Inflammation

- Activation and priming
- Leukocyte adhesion
- Phagocytosis
- Inflammatory mediators

Cassuto, Acta Anaesthesiol Scan 2006
IV Lidocaine – Inflammation

- Inflammatory mediators

⇒ Virtually every level of the inflammatory cascade is affected by LA!

Cassuto, Acta Anaesthesiol Scan 2006
IV Lidocaine – Inflammation

IV lidocaine => profound effects on perioperative inflammatory response:

- Decreased priming of neutrophils
  - Priming => activation => production of ROS
    = basis of inflammatory cascade triggered by surgery

- NO decreased activation of neutrophils!
  => prevention of OVERactivation of inflammatory cascade (SSI ... )
Clinical implications:
- Fx on vascular hyperpermeability and oedema formation:
  - Small gut obstruction (Nellgard 1993 and 1996)
  - Skin burns (Jönsson 1998)
  - Extravasation of lung water (Erjefäldt 1995 and 1991)
- Lung injury
- Septic shock
- Myocardial ischemia
- Anti-microbial effects

Cassuto, Acta Anaesthesiol Scan 2006
IV Lidocaine - Inflammation

⇒ Clinical implications:
- Ex on vascular hyperpermeability and oedema formation
- Acute lung injury:
  - ↓ of thiourea induced ALI in rats
  - ↓ ALO in reperfused rat lungs
  - ↓ Endotoxin-induced ALI in rabbits
  - Better graft function in allotransplanted dogs
  - Prophylactic effect on hyperoxic ALI
  - ↓ ALI in acute pancreatitis
  - ↓ Fibrosis in bleomycin-induced ALI
  - ↓ ALO in isolated post-ischemic rat lung
- Septic shock
- Myocardial ischemia
- Anti-microbial effects

Possible mechanism?
↓ release of free radicals, proteases and lysosomal enzymes by neutrophils

Cassuto, Acta Anaesthesiol Scan 2006
IV Lidocaine – Inflammation

⇒ Clinical implications:
- Fix on vascular hyperpermeability and oedema formation
- Acute lung injury
- Septic shock: experiments by Fletcher et al:
  - ↑ survival in endotoxin-induced shock in dogs and baboons
  - ↓ capillary leak and diaphragmatic dysfunction in septic hamsters
  BUT ALSO...
  - ↑ hypoglycemia (but improved glc-utilisation), lactic acidosis, hypoalbuminemia, ...
- Myocardial ischemia
- Anti-microbial effects

Possible mechanism?
↓ eicosanoid synthesis

Cassuto, Acta Anaesthesiol Scan 2006
IV Lidocaine – Inflammation

⇒ Clinical implications:
- Fx on vascular hyperpermeability and oedema formation
- Acute lung injury
- Septic shock
- Myocardial ischemia:
  - Protective effects against ischemia and reperfusion injury
  - Reduced AMI size
- Anti-microbial effects

Possible mechanism?
- ↓ neutrophil recruitment and activation ⇒ ↓ release of free radicals
- Prevention of ion fluxes associated with tissue damage
- ↓ lipid peroxidation products from reperfused myocardium

Cassuto, Acta Anaesthesiol Scan 2006
IV Lidocaine – Inflammation

Clinical implications:
- Fx on vascular hyperpermeability and oedema formation
- Acute lung injury
- Septic shock
- Myocardial ischemia
- Anti-microbial effects:
  - Wright 2008: antiviral, antibacterial, antifungal effects

Cassuto, Acta Anaesthesiol Scan 2006
IV Lidocaine – Inflammation

The anti-inflammatory effects of IV lidocaine

INFLAMMATION

- Pain
- Bowel function
- Cancer
- Lung injury
- QoR
IV Lidocaine – Cancer

- Effects of anesthesia on prognosis after cancer surgery = hot topic
  Focus on LRA: promising evidence, but mainly retrospective

- Amide-linked LA: antiproliferative and cytotoxic effects *in vitro*:
  - Martinsson 1999 (colon adenocarcinoma)
  - Karniel 2000 (melanoma)
  - Arai 2002 (lymphoma)
  - ...

- *In vivo*: IV hypnotics, opioids, VA, ...
IV Lidocaine – Cancer

Role of inflammation on tumor growth: +

Lee et al, Int J Cancer. 2012
Role of inflammation on tumor growth:

Mitra et al, Expert Reviews in Molecular Medicine 2003

=> Defence against cancer relies on intact immune response by NK cells

Mitra et al, Expert Reviews in Molecular Medicine 2003
IV Lidocaine – Cancer

Role of inflammation on tumor growth

- Many similarities between tumor growth and tissue repair: Local inflammation and cellular proliferation:
  - Activation and migration of mesenchymal stem cells and fibroblasts
  - Angiogenesis
  - Resistance to apoptosis

- Inflammatory system: cytokines, chemokines, PGIs, COX, ...

- Clear evidence in chronic inflammation: Colitis Ulcerosa, Refluxesophagitis, Hepatitis, ...

- What about surgically induced inflammation?

Gottschalk 2010
IV Lidocaine – Cancer

Role of inflammation on tumor growth

Not so clear in acute, surgically induced, inflammation?

- Many carcinogenic factors present in perioperative period:
  - Opioids
  - Immunosuppressive fx of transfusion
  - Profound suppression of NK cytotoxic activity in perioperative period => decreased cellular defense against tumor cells
  - Surgical stress
  - Cellular contamination
  - Local and systemic release of GF’s (EGF and VEGF)
  - ‘tumor boost’: release and proliferation of mesenchymal stem cells

- Inflammation not the only mechanism by which LA can suppress tumor growth

Gottschalk et al, Anesth Analg 2010
Lin et al, BJA 2011
IV Lidocaine – Cancer

Role of intravenous LA in cancer recurrence

Indirect effects:
- Reduced inflammation
- Opioid sparing
- Surgical stress response?
- Sensitizing for chemotherapeutics and hyperthermia

Direct effects:
- Cytotoxic?
- Decreased autophosphorylation of tyrosine kinases (EGFR, Src, ...)
- Demethylation of DNA
- Antiproliferative fx on mesenchymal stem cells

Opioids promote:
- Angiogenesis
- Migration and proliferation of tumor cells

Piegeler et al, Anesthesiology 2011

Opioids suppress:
- Cell mediated and humoral immunity (NK cell activity, °cytokines, phagocytosis, AB production)

Snyder et al, BJA 2010
IV Lidocaine – Cancer

Role of intravenous LA in cancer recurrence

Indirect effects:
- Reduced inflammation
- Opioid sparing
- Surgical stress response?
- Sensitizing for chemotherapeutics and hyperthermia

Direct effects:
- Cytotoxic?
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- Demethylation of DNA
- Antiproliferative fx on mesenchymal stem cells

Surgical stress increases susceptilibity to metastatic formation:
Mechanism? - HPA axis

Not sure if IV LA suppress SSR
IV Lidocaine – Cancer

Role of intravenous LA in cancer recurrence

Indirect effects:
- Reduced inflammation
- Opioid sparing
- Surgical stress response?
- Sensitizing for chemotherapeutics and hyperthermia

Direct effects:
- Cytotoxic?
- Decreased autophosphorylation of tyrosine kinases (e.g., EGFR, Src, …)
- Demethylation of DNA
- Antiproliferative fx on mesenchymal stem cells

Lidocaine has sensitizing effects on bleomycin-induced toxicity
Kennedy et al, Int J Radiat Oncol Biol Phys 1986
IV Lidocaine – Cancer

Role of intravenous LA in cancer recurrence

Indirect effects:
- Reduced inflammation
- Opioid sparing
- Surgical stresss response?
- Sensitizing for chemotherapeutics and hyperthermia

Direct effects:
- Cytotoxic?
- Decreased autophosphorylation of tyrosine kinases (EGFR, Src, …)
- Demethylation of DNA
- Antiproliferative fx on mesenchymal cells

Systemic lidocaine enhanced hyperthermia induced tumor regression in transplantable murine tumor cells: Mechanism possibly involves interference with cell membrane stability

Robin et al, Cancer Research 1993
IV Lidocaine – Cancer

Role of intravenous LA in cancer recurrence

Indirect effects:
- Reduced inflammation
- Opioid sparing
- Surgical stress response?
- Sensitizing for chemotherapeutics and hyperthermia

Direct effects:
- Cytotoxic?
- Decreased autophosphorylation of tyrosine kinases (EGFR, Src, ...)
- Demethylation of DNA
- Antiproliferative fx on mesenchymal

Known toxic effects probably not important in plasmalevels seen after IV administration
IV Lidocaine – Cancer

Role of intravenous LA in cancer recurrence

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- Reduced inflammation
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Phosphorylation of TK = crucial rol in regulating cellular proliferation or differentiation of epithelial cells and tumors => potential target for anticancer therapies

Sakaguchi, Anesth Analg 2006
IV Lidocaine – Cancer

Role of intravenous LA in cancer recurrence

Indirect effects:
- Reduced inflammation
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Lidocaine = DNA-demethylating agent
Methylation of DNA => down-regulation of tumor suppressor genes (e.g. breast cancer)

Lirk et al, BJA 2012
IV Lidocaine – Cancer

Role of intravenous LA in cancer recurrence

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LA impaired proliferation, differentiation (...) and were cytotoxic to murine mesenchymal stem cells => possible beneficial antitumor effects BUT possible detrimental effects on wound healing

Lucchinetti et al, Anesthesiology 2012
IV Lidocaine – Cancer

Role of intravenous LA in cancer recurrence

Indirect effects:
- Reduced inflammation
- Opioid sparing

=> Promising effects *in vitro* and in experimentally induced tumors in animals, but no clinical studies in humans to date

- Cytotoxic?
- Decreased autophosphorylation of tyrosine kinases (EGFR, Src, ...)
- Demethylation of DNA
- Antiproliferative fx on mesenchymal stem cells
IV Lidocaine

So what’s not to like?
- Toxicity and pharmokinetics:
  - Asthma (Chang 2007)
  - More infection due to anti-inflammatory effect?
  - Decreased wound healing
IV Lidocaine

So what’s not to like?
- Toxicity and pharmacokinetics:
  - $T\frac{1}{2}$ +/- 100 min after bolus
  - Plasma clearance 10 ml/kg/min
  - $V_d$ 0.5 L/kg
  - Metabolized by liver, renal excretion
    - High hepatic ER
    - CYP3A4
  - Significant context-sensitive $T\frac{1}{2}$
    - 48h: $T\frac{1}{2}$ up to 4 hrs
- Asthma (Chang 2007)
  More infection due to anti-inflammatory effect?
- Decreased wound healing
So what’s not to like?

- **Toxicity and pharmacokinetics:**
  - Toxic plasma levels > 5 mcg/ml (> 3 mg/kg/h)
  - Typical values 1-2 mcg/ml (McCarthy)
  - Toxic events not systematically reported throughout studies
  - No ‘gold standard’ dose regimen
  - Liver function! (CYP3A4)
  - Therapeutic dose range 2-10 mcg/ml (Tanelian and MacIver)
    => ~

- Asthma (Chang 2007)
- More infection due to anti-inflammatory effect?
- Decreased wound healing
So what’s not to like?

- Toxicity and pharmokinetics:

- **Asthma** (Chang 2007):
  - 15 asthmatic volunteers under baseline conditions
  - IV lidocaine, no control group (!)
  - FEV1 and CT graphic airway luminal diameter
  - **RESULTS:**
    - Decrease in FEV1 and ALD with lidocaine
  - More infection due to anti-inflammatory effect?
  - Decreased wound healing
So what’s not to like?

- Toxicity and pharmokinetics:

- **Asthma (Chang 2007):**
  
  - **CONCERNS:**
    - Only 15 patients, no control group, no blinding
    - No asthmatic events
    - No pathophysiologic mechanism

  "While the administration of lidocaine can prevent intubation-induced bronchospasm in some patients with asthma, it is not always effective. Future studies should focus on the structural changes in the airways that lead to this paradoxical response"
So what’s not to like?

- Toxicity and pharmacokinetics:
- Asthma (Chang 2007)
- **More infection due to anti-inflammatory effect?**
  - Fischer 2001, Holmann 2001:
    - $\downarrow$ priming of neutrophils $\Rightarrow$ no inhibition of activation BUT inhibition of OVERactivation of inflammation
    - Favorable effects in (experimentally induced) sepsis
    - Anti-microbial properties (Wright 2008)
- Decreased wound healing
IV Lidocaine

So what’s not to like?

- Toxicity and pharmacokinetics:
- Asthma (Chang 2007)
- More infection due to anti-inflammatory effect?
- **Decreased wound healing:**
  - Reduction of mobilisation and differentiation of mesenchymal stem cells might decrease wound healing
  - *In vitro* - No clinical evidence
Conclusions

- Perioperative intravenous lidocaine...
  - ... reduces acute pain, postoperative ileus, PONV and LOHS in abdominal surgery
  - ... has anti-inflammatory effects
  - ... possibly reduces incidence of cancer recurrence

- Favorable safety margin

- Ideal dosing unclear, continuous postop infusion recommended (24 hrs)