NEONATAL SPINAL ANAESTHESIA
History

- Tyrell-Gray: 1909, 300 spinals in infants
- Berkowitz: 1950, 350 patients (9<4y) procaine 45-60min, nupercaine >60min
- Abajian: 1984-1999, 1000 spinals
Postoperative apnoea in former premature infants

Cote et al, Anaesthesiology 1995
Causes and significance

- Central, obstructive, mixed
- Immature respiratory control
- Obstruction at nasopharynx or aryepiglottic folds
- Nasal breathing
- Propensity to respond to airway obstruction with apnoea
- Postoperative pain
- Shift of work from intercostals to diaphragm
- Bradycardic laryngeal reflex
- Bradycardia with hypoxaemia
- Reduced cerebral perfusion with Bradycardia
- Most apnoeas self limiting
- Potential death
Spinal vs GA apnoea rates

- **Krane et al, Anaes & Analg 1995**
  - Tetracaine vs halothane
  - Desaturation and bradycardia post GA

- **Kunst et al, Can J Anaes 1998**
  - Bupivacaine vs halothane
  - 50% apnoea both groups

- **O’Brien et al, BJA 1998**
  - Des/ sevo/ halothane
  - Extubation 6-10 min earlier with des
Indications

- Lower abdominal surgery
- Upper abdominal surgery
  - Gastroschisis repair
  - Colostomy for imperforate anus
- Meningomyelocoele repair
- PDA ligation
Anatomy

- Lateral decubitus or sitting position
  - Neck extended
  - Modified lateral in sick neonate
- Conus medullaris L3
- Iliac crest L4-5, L5-S1
- Laminae poorly calcified
- Ligamentum flavum soft
- Intrathecal space 1.4 cm (adult 4 cm)
  - Mean depth = 0.03 x height (cm)
    Craig et al, Arch Dis Child 1997
- Dead space 25 G needle 0.04 ml
Physiology

- CSF volume term 14 ml/kg (adult 2 ml/kg) and turnover high
- CSF distribution spinal relative to cerebral 50% (adult 25%)
- Haemodynamic stability even when high thoracic block and without volume load
  - Spinal induced diminished vagal tone
  - Small lower limb capacitance
  - Low resting sympathetic tone

  Oberlander et al., Anes & Analg 1995

- Paradoxical chest wall motion
  - Inhibition coordinated intercostal muscle activity

  Pascucci et al., J Appl Physiol 1990

- High block from leg elevation
Pharmacology

- **Formulation**
  - Hydrochloride salt for H2O solubility
  - Glucose
  - Adrenaline, preservative (Na metabisulphite, methyl parahydroxybenzoate), fungicide- arachnoiditis

- **Mechanism of action**
  - Unionised drug passes through lipid membrane
  - Protonated form in axoplasm binds to internal surface Na channel
  - Channel remains in inactive state
  - Frequency dependent blockade due to attraction to ‘open’ Na channels

- **Physicochemistry**
  - Weak bases with pKa>7.4; exist predominantly in ionized form at neutral pH
  - Ester -CO.O- or amide -NH.CO- link between lipophilic aromatic group and hydrophilic group
Pharmacology (cont)

- R3 = CH3 Mepivacaine, C3H7 Ropivacaine, C4H9 Bupivacaine
Pharmacology (cont)

- Dose/kg 5-fold higher than adult
  - Tetracaine
    - <1 m: 0.4 - 0.5 mg/kg
    - 3-24 m: 0.2 - 0.3 mg/kg
  - Bupivacaine: 0.5 - 1 mg/kg
  - Levo bupivacaine: 1 mg/kg
  - Ropivacaine: ? 1.5 mg/kg

- Duration ¼ to ½ adult
  - Depends on slow vascular absorption

- Sensory level for testicular and peritoneal traction higher than for hernial sac dissection
Bupivacaine 0.5%, 0.25%

- Levo isoform is active; dextro causes toxicity
- High protein binding 95% (alpha1-acid GP and albumin)
  - Long duration
  - Slow dissociation from Na channels
- pKa 8.1; 15% unionised at pH 7.4
  - Long latency
- Lipid sol due to butyl gp 30x mepivacaine
  - High potency
Ropivacaine 1%, 0.75%

- 99% pure S enantiomer
- Protein binding 94%, pKa 8.1%
- Lower lipid sol than bupivacaine
  - Lower potency
  - ? Less penetration A beta motor fibres
  - ? Less diffusion away from A delta and C fibres in low concentration
    - Sensory block epidural 23-45 min longer, peripheral block 2 hr longer
    - Differential block greater than bupivacaine
      - ? Shorter latency due to increased concentration gradient
- Intrinsic vasoconstriction
  - ? Less systemic absorption and toxicity
  - ? Longer sensory block
- ? Drug-receptor interaction
  - ? Shorter motor block
RCH study

**ROPIVACAINE DOSE RANGE FOR NEONATAL SPINAL ANAESTHESIA**

Prospective study of 50 ex prem neonates or infants < 60 weeks post conceptual age having elective inguinal hernia repair at RCH

- 231 hernia repairs in appropriate age group at RCH January 2003 - January 2004
- 55% spinal alone (bupivacaine)

- Ropivacaine 0.5%, starting dose 1.25 mg/kg, intervals 0.25 mg/kg
RCH study: Outcomes

- **Primary**
  - Onset time and adequacy of surgical anaesthesia determined by response to surgical incision and increase BP and HR < 20% baseline

- **Secondary**
  - Duration of motor block measured by modified Bromage and FLACC scores
  - Study completion after 2 hour recovery
RCH study: Exclusion criteria

- Significant hepatic or renal disease
- Severe cyanosis
- Anticoagulants
- Coagulopathy
- Known contraindication to LP
- 1kg < Weight > 4kg
- CYP3A4 inducers (phenytoin, phenobarbitone) and inhibitors (erythromycin, verapamil)
- Parental refusal
- Enrolled other study
RCH study: Design

- Sequential allocation [Dixon 1991]: up-down method, clusters doses around ED50 (MLAC, EC50)
- Blinded patient and research assistant
- Sample size 50 calculated from SD of ED50 (MLAC) from previous studies; SEM (20% SD) = SD/square root N
- Homogenous study population
- Dose intervals equivalent to one SD of the log dose-response curve
- Precise estimate of ED50
- Logistic regression to estimate ED95
- Wider CI for ED95
Up-down method

- Deng et al, Anes & Analg 2002
Dose-response curve

- Michaelis Menten equation
  \[ E = \frac{E_{\text{max}} \times C}{E_{\text{C50}} + C} \]
Log dose-response curve
Levobupivacaine study 2004: Results

- Frawley et al, Ped Anes 2004
- ED50 0.48 mg/kg (0.42-0.54)
- ED95 1.14 mg/kg (0.78-1.5)
- Rapid onset
- Block significantly shorter at 0.5 mg/kg
- One procedure exceeding 73 min outlasted block at 0.75 mg/kg
- One patient had upper limb weakness with altered respiratory pattern at 1.25 mg/kg
## Cost

<table>
<thead>
<tr>
<th></th>
<th>Unit cost $</th>
<th>Annual cost $</th>
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<tbody>
<tr>
<td>Bupivacaine</td>
<td>1.60</td>
<td>9,750</td>
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<tr>
<td>Bup Ad</td>
<td>9.57</td>
<td>32,850</td>
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<tr>
<td>Rop 0.75%</td>
<td>6.41</td>
<td>790</td>
</tr>
<tr>
<td>Levo 0.5%</td>
<td>6.26</td>
<td>626</td>
</tr>
<tr>
<td>Levo 0.25%</td>
<td>5.25</td>
<td>1,219</td>
</tr>
</tbody>
</table>

- Replacement Bup 0.5% with Levo 0.5% $28,400/yr
- Replacement Bup with Rop in US obstetric anaesthesia $15,000,000/yr
Bupivacaine toxicity

- Bupivacaine 0.75% withdrawn
  - Pregnant sensitivity
  - CC:CNS concentration ratio 1.6 (ropivacaine 2.5)
  - Slow dissociation from cardiac Na channels
  - Precipitous hypotension, cardiac dysrhythmias and AV block
  - Refractory to resuscitation
- No maternal deaths from cardiotoxicity since 1984 in over 23,000,000 labour epidurals
- Auroy et al, Anesthesiology 1997
  - Cardiac arrest following epidural 1/10,000
- Relative risk makes ropivacaine appealing while absolute risk low
Intravascular injection

- Incidence 1/4000, less in neonates  
  Giaufre et al, Anes Analg 1996)
- Adults tolerate 0.3 mg/L free bupivacaine (3-5 ug/ml total conc) or 0.6 mg/L free ropivacaine  
  Knudsen et al, BJA 1997
- Plasma bupivacaine newborn spinal  
  - 0.31 ug/ml plain (87% bound),  
    0.25 ug/ml with adren (81% bound)
- Tests  
  - Aspiration in collapsed vein may give false negative  
  - Tachycardia following adrenaline may lack specificity
Low birth weight infants (<1500 g)

- Rapid rate of rise in neonates
  - High free drug levels
  - Limited hepatic metabolism

- Compared with older neonates
  - CL $\frac{1}{2}$ (8 vs 17 ml/kg/hr)
  - Vd increased
  - Elimination t$\frac{1}{2}$ 4x (453 vs 102 min)

- Unpredictable levels

- Accumulation with redosing

Weston et al, Paed Anaes 1995
CNS toxicity

- Sedation seen with regional anaesthesia may represent CNS toxicity
- Epileptic activity clinically or EEG with awake caudal anaesthesia bupivacaine 3mg/kg with adrenaline 5 ug/ml
- Total plasma bupivacaine 0.33-0.76 ug/ml
- Increased CNS/CVS sensitivity neonates
  Breschen et al, Anaesthetist 1998
Epidural haematoma

- Incidence 1:200,000
- Associations
  - Coagulopathy, epidural > spinal, bloody tap, catheter insertion or withdrawal, spontaneous
- Features
  - Variable back pain, radicular pain 24-48 h after insertion
  - Bladder, bowel dysfunction, new weakness
  - Absence of block regression
    - Crowe et al, Anaes 2001
- Need for MRI and surgical decompression
  - Within 8-12 h for good neurologic recovery
    - Morgan, Mikhail et al
Epidural abscess

- Incidence 1:500,000
- Median onset of symptoms 5 days, but possible from 1-60 days
- Site erythema and tenderness, new back ache and increasing leg weakness, loss of sensation and sphincter control
- May present with paraplegia alone
  Kindler at al, 1998

- Duration of spinal anaesthesia
  - Bupivacaine 90-120 min (100-150 min with adren)
  - Ropivacaine 90-120 min