Epidural and CSF Pharmacokinetics of Drugs

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What is Pharmacokinetics

- Part of Pharmacology

- The term pharmacokinetics comes from the Greek words:
  - pharmakon - drug or medicine
  - kinitiki / kinisi – procedure of “movement”

- What the body does to the drug

- Relationship between drug dose & its concentration of effector sites
Pharmacokinetics

- **Hypothesis**
  Drug Action: requires presence of a certain concentration in the fluid bathing the target tissue.

- The magnitude of response (good or bad) depends on concentration of the drug at the site of action
### Table 1. Chronology.

<table>
<thead>
<tr>
<th>Inventor/Locator</th>
<th>Year</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domenico Cotugno</td>
<td>1764</td>
<td>Described cerebrospinal fluid</td>
</tr>
<tr>
<td>Friedrich Serturk</td>
<td>1803</td>
<td>Isolated morphine</td>
</tr>
<tr>
<td>Francis Rynd</td>
<td>1845</td>
<td>Administered morphine to peripheral nerve</td>
</tr>
<tr>
<td>Charles-Gabriel Pravaz</td>
<td>1850s</td>
<td>Invented the syringe</td>
</tr>
<tr>
<td>Alexander Wood</td>
<td>1855</td>
<td>Invented the hypodermic needle</td>
</tr>
<tr>
<td>Carl Koller</td>
<td>1884</td>
<td>Discovered cocaine</td>
</tr>
<tr>
<td>James Corning</td>
<td>1885</td>
<td>Developed epidural anaesthesia</td>
</tr>
<tr>
<td>Walter Wynter and Heinrich Quinke</td>
<td>1890</td>
<td>Performed dural puncture</td>
</tr>
<tr>
<td>August Bier</td>
<td>1898</td>
<td>Performed intrathecal anaesthesia</td>
</tr>
<tr>
<td>Nicolae Racoviceanu-Pitesti</td>
<td>1900</td>
<td>Administered intrathecal morphine</td>
</tr>
<tr>
<td>Oscar Kreis</td>
<td>1900</td>
<td>Utilized epidural for childbirth</td>
</tr>
<tr>
<td>Fernand Cathelin</td>
<td>1901</td>
<td>Developed caudal anaesthesia</td>
</tr>
<tr>
<td>Thomas Jonnesco</td>
<td>1919</td>
<td>First textbook of intrathecal anesthesia</td>
</tr>
<tr>
<td>Arthur Barker</td>
<td>1920</td>
<td>Created glass model of spinal canal</td>
</tr>
<tr>
<td>Eugen Aburel</td>
<td>1931</td>
<td>Instituted continuous epidural for childbirth</td>
</tr>
<tr>
<td>A. Soresi</td>
<td>1937</td>
<td>Developed combined intrathecal–epidural anaesthesia</td>
</tr>
<tr>
<td>Mario Dogliotti</td>
<td>1939</td>
<td>Considered ‘father’ of modern epidural anaesthesia</td>
</tr>
<tr>
<td>William Lemon</td>
<td>1940</td>
<td>Developed continuous spinal anaesthesia</td>
</tr>
<tr>
<td>Edward Tuohy</td>
<td>1944</td>
<td>Invented the Tuohy needle</td>
</tr>
<tr>
<td>Roman-Vega</td>
<td>1946</td>
<td>Developed the saddle-block</td>
</tr>
<tr>
<td>Philip Bromage</td>
<td>1978</td>
<td>Textbook of ‘Epidural Anesthesia’</td>
</tr>
<tr>
<td>Murat Behar</td>
<td>1979</td>
<td>Administered epidural morphine</td>
</tr>
<tr>
<td>Vittorio Pasqualucci</td>
<td>1981</td>
<td>Used epidural morphine for myocardial infarction pain</td>
</tr>
<tr>
<td>Bjorn Sjostrom</td>
<td>1981</td>
<td>Used epidural PCA with morphine</td>
</tr>
<tr>
<td>Nicolae Mirea</td>
<td>1982</td>
<td>Used meperidine for intrathecal anaesthesia</td>
</tr>
</tbody>
</table>
Neuraxial Drug Administration

- Local Anaesthetics
- Vasoconstrictors
- Opioids
- a2 – adrenergic agonists
- NMDA receptor antagonists (ketamine)
- Midazolam
- Baclofen
- Anticholinesterase drugs, cholinergic agonists
- Adenosine
- Steroids

- Calcitonin
- Somatostatin
- Octreotide
- Antioxidants
- Ziconotide
Epidural & CSF Pharmacokinetics

- **Pharmacology of spinal drug delivery:** subject of *innumerable* clinical and animal studies

- **Pharmacokinetics of spinal drugs:**
  - many studies in literature
  - animal models
  - very few data for humans

- **Up to now: Indirect Study Approach**
  - inability to sample epidural space
  - Measurement of drug C: plasma & CSF (occasionally)
  - not direct experimental evidence
  - questionable validity of knowledge

*Bernards CM et al.*
*Anesthesiology* 2003; 99: 455 – 465
Spinal Drugs Administration

**SPINAL DRUGS**

**Epidurally**
- Single – Shot / Bolus
- Continuous Infusion

**Intrathecally**
- Single – Shot / Bolus
- Continuous Infusion
Spinal Drugs Pharmacokinetics

- Changes in drug concentration over time in various compartments
  - Blood
  - Epidural Space
  - CSF
  - Effector Site: Spinal Cord

DETERMINED
physicochemical properties of drug
multitude of biologic functions
SPINAL OPIOIDS

Pharmacokinetics
Spinal Drugs Administration

**Aim:**

- Intense Spinal Analgesia
- Spinally Mediated Analgesia
  without dose limiting side – effects associated with systemic administration

**Misconception:**

- any drug
  - epidurally
  - intrathecally

- Resultant analgesia **not always** mediated by a spinally selective mechanism

*Bernards CM et al. Anesthesiology 2003; 99: 455 – 465*
Spinal Opioids

- Commonality of mechanism of action
- Differences in pharmacokinetics & pharmacodynamics
- Opioids differ in their ability to reach opioid receptors

**Net Analgesic Effect:**

The result of numerous processes prior to G – protein activation

*Bernards CM, ASA Refresh Course Lectures, Seattle, 2002*
Mechanism of Action - Bioavailability

- Effect depends on:
  - **affinity**
  - **ability to reach receptors**

- Penetration of neural tissue: *The rate limiting step*

- Factors affecting **transmembrane movements**
  - pKa (the lower pK, the greater fraction of uncharged form at pH of 7.4)
  - Molecular Weight
  - Protein Binding
  - Lipid Solubility
Bioavailability of spinally administered drug

- The fraction of the dose of a drug (F) given spinally (epidural / intrathecal space) that reaches the intended site of action

\[ F = \frac{\text{amt. of drug that reaches site of action}}{\text{Dose administered}} \]

\[ F = \frac{\text{AUC}}{\text{Dose}} \]
Pharmacokinetics

- Administration
- Absorption
- Distribution
- Binding - Bioavailability
- Inactivation - Metabolism (Biotransformation)
- Elimination - Excretion
Pharmacokinetics

Key Terms
-Onset of Action
-Peak Effect
-Duration of Action
EPIDURAL DRUGS – ROUTES OF UPTAKE

POTENTIAL FATES

EPIDURAL ADMINISTRATION

- Paraspinal Muscle Space through intervertabral foramina
- Diffusion into ligaments that border epidural space
- Vascular Uptake by Epidural Vessels
- Diffusion across meninges (CSF mixture)
- Diffusion to lipophilic tissues in epidural space (epidural fat)
Target of Action: Reaching Receptors

- Epidurally administered drugs must travel through:
  - dura matter
  - arachnoid matter
  - CSF
  - pia matter
  - white matter
  - gray matter → dorsal horn

- Competing pathways
  - Uptake into epidural fat
  - Uptake into systemic circulation
Target of Action: Reaching Receptors

- Intrathecally administered drugs must travel through:
  - CSF
  - pia matter
  - white matter
  - gray matter  \(\rightarrow\) dorsal horn

- Competing pathways
  - Diffusion into epidural space
  - Uptake into systemic circulation
Absorption

- Absorption Mechanics
- Absorption Principles
- Absorption Barriers
Distribution

Generalized distribution of a drug controls

- the movement of a drug by its effect on ionization ratios
- how long a drug acts
- how intense are its effects
- side effects produced

Is there a magic bullet?
Absorption – Distribution

Rate & Extent depend upon

- Chemical structure of drug
- Rate of blood flow
- Ease of transport through membrane
- Binding of drug to proteins in blood
- Elimination processes

THE ONLY MECHANISM BY WHICH DRUGS REDISTRIBUTE FROM ES TO SC: Diffusion through spinal meninges

Bernards CM et al. Anesthesiology 1994; 80: 872 – 878
Curr Opin Anesthesiol 2003; 17: 441 - 447
Drug
Physicochemical properties

- $P_{ka}$
- Partition coefficient
  - Lipid Solubility
  - Octanol:Buffer distribution coefficient
- Permeability coefficient
# Relative Solubilities

<table>
<thead>
<tr>
<th>Drug pH:</th>
<th>Solution pH:</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 7 (Acid)</td>
<td>Un-ionized, Fat soluble</td>
</tr>
<tr>
<td>&gt; 7 (Base)</td>
<td>Ionized, Water soluble</td>
</tr>
<tr>
<td>OPIOID</td>
<td>Partition Coefficient</td>
</tr>
<tr>
<td>---------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Morphine</td>
<td>1.0</td>
</tr>
<tr>
<td>Meperidine</td>
<td>38.8</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>110</td>
</tr>
<tr>
<td>Alfentany</td>
<td>129</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>180</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>560</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>813</td>
</tr>
</tbody>
</table>

- **Hydrophilic Drugs**
- **Lipophilic Drugs**
Well characterized in vivo pig model

- Microdialysis Technique
- Continuous Samples
- Bolus Epidural: morphine, alfentanil, fentanyl, sufentanil

- Quantification of Redistribution
  - Epidural Space
  - Intrathecal Space
  - Systemic Venous Plasma
  - Epidural Venous Plasma
Lipid Solubility & Mean Residence Time (MRT) in epidural space

LINEAR RELATIONSHIP

Figure 1. Relationship between opioid mean residence time in the epidural space and opioid lipid solubility (octanol:buffer distribution coefficient)

\[
y = 42 + 0.058x \quad R = 0.98
\]

Bernards CM et al. Anesthesiology 2003; 99: 455 – 465
Curr Opin Anesthesiol 2003; 17: 441 - 447
Lipid Solubility & Terminal Elimination Half – Life in epidural space

**Figure 2.** Relationship between opioid lipid solubility (octanol : buffer<sub>7.4</sub> distribution coefficient) and terminal elimination half-life in the epidural space

\[ y = 73 + 0.054x \quad R = 0.93 \]

*Bernards CM et al.*
Anesthesiology 2003; 99: 455 – 465

*Curr Opin Anesthesiol 2003; 17: 441 - 447*
Lipid Solubility

&

Dose – Normalized C in epidural fat (lumbar ES)

LINEAR RELATIONSHIP
Epidural Administration of Drugs
Lipid Solubility

**Lipid Soluble Drugs**

- Spend a significantly longer time in epidural space
- Require a significantly longer time to be eliminated from epidural space
- Greater Partitioning in epidural fat
- Ongoing Slow Release back into the epidural space

*Bernards CM et al.*
*Anesthesiology* 2003; 99: 455 – 465
Lipid Soluble Opioids

- Lower C in CSF
- Low CSF Bioavailability
- A larger proportion of morphine reaches CSF in comparison with other more lipid soluble opioids
- Rapid clearance from Epidural Space to circulation
  - Decreased amount of drug available at the spinal level
  - Systemic effects

Bernards CM et al.
Anesthesiology 2003; 99: 455 – 465
Curr Opin Anesthesiol 2003; 17: 441 - 447

Figure 4. Dose-normalized area under the curve (AUC) for morphine, alfentanil, fentanyl and sufentanil in the spinal cerebrospinal fluid (CSF) opposite the site of epidural administration.
Epinephrine Action

In Lumbar ES

Increased MRT morphine

Decreased MRT fentanyl sufentanil

No effect on elimination of morphine in ES

Decreased terminal elimination half life of fentanyl sufentanil
Increased AUC concentration time in the intrathecal space of morphine

No effects in pharmacokinetics of other opioids in lumbar intrathecal space
Absorption & Distribution Principles
Opioids from Epidural Space to CSF & SC

- General principle: 
  **Simple Diffusion**
  Concentration Gradient

- But in Epidural Space
  Additionally
  Pulsation with systole
  Kinetic Energy to opioids molecules
  **Motion production**

*Bernards CM et al.*
*Curr Opin Anesthesiol 2003; 17: 441 - 447*
Absorption Principles
Opioids from Epidural Space to CSF & SC

■ **Preferential Diffusion**
  - arachnoid granulations of spinal nerve root cuff

■ **Uptake**
  - radicular arteries traversing epidural space
  - vascular distribution to SC

■ **Absorption influenced**
  amount of **blood flow** at the site of administration

■ **Diffusion** through spinal meninges

*Bernards CM et al.* Curr Opin Anesthesiol 2003; 17: 441 - 447
Absorption Principles
Opioids from Epidural Space to CSF & SC

- **Differential Permeability through Meninges**

- Meningeal Permeability

- Significant Differences of clinically available opioids

- Not important role in absorption

*Bernards CM et al. Anesthesiology 1994; 80: 872 – 878*
Bi – Phasical Relation

of meningeal permeability coefficients & lipid solubility of opioids

Bernards CM et al. Anesthesiology 1991; 75: 827 – 832
Absorption Barriers
DURA MATTER

- The **thickest** of spinal meninges
- Selective **Physical Barrier**
- **Not important** Permeability Barrier
- **Not important role** in Opioid Distribution
- Important Site of **Drug Clearance**
  - Inner Surface of Dura
  - Rich Capillary Network
- Effective **Clearance Barrier**
  drugs diffusing: from Epidural to Intrathecal Space
- **Site of Clearance**
  Epidural drugs into plasma
- drug available at the spinal level
- Produces systemic effects (dose-dependent)

Ummerhoffer WC et al. *Anesthesiology* 1998; 88: 1259 - 1265
Permeability of morphine through the individual spinal meninges of the monkey (macaca nemestrina)

Bernards CM & Hill HF. Anesthesiology, 1990; 73: 1214 – 1219
Absorption Barrier
Arachnoid MATTER

Arachnoid matter is the principle meningeal barrier

- more than 90% of the resistance to drug diffusion
- 6 -10 layers of tightly adherent cells
- Repeated aqueous:lipid interfaces
- **Metabolic Barrier**
  - Contains enzymes that metabolize substances
- **Arachnoid Granulations /Villi**
  - Movement of substances outwards CSF
  - Active Transport via pinocytosis / No open pores
  - Transport into CSF does not occur
Absorption Barrier
Arachnoid MATTER

*Arachnoid matter as a METABOLIC BARRIER*

- Multiple enzyme systems
  - Cytochrome P – 450
  - Glucoronyl transferase
- Expression of enzymes metabolizing neurotransmitters
  - Epinephrine
  - Norepinephrine
  - Acetylcholine
  - Neuropeptides
- *Acetylcholinesterase activity* = SC
- ??? Analgesic effect of spinal neostigmine

*Ummerhoffer WC et al.* Anesthesiology 1998; 88: 1259 - 1265
Spinal Drugs
Cross Dural Membrane
Mix with CSF
The Fate of Intrathecal Drugs

- Opioids that reach CSF: by direct injection or from ES
  **Behave Identically**

- **Diffusion** into the epidural space → systemic circulation
  - Amount of drug administered IT: LOST
  - Major Route of elimination for IT drugs

- **Diffusion** into the spinal cord → systemic circulation

- Rostral spread of hydrophilic opioids
  More rapid vs lipophilic
The Fate of Intrathecal Drugs

Rostral spread:

- **Simple Diffusion**
  - Temperature
  - Molecular Weight (square root)

- **Bulk Flow – Movement**
  - Energy from the pulsatile flow of blood into CNS
  - Transient increase in brain volume
  - Pulsing brain acts like plunger
  - CSF force down dorsally and up ventrally

- As CSF moves it carries molecules suspended into it

- **Baricity** of injectate: no effect
Comparative Spinal Distribution and Clearance Kinetics of Intrathecally Administered Morphine, Fentanyl, Alfentanil, and Sufentanil

Wolfgang C. Ummenofer, M.D.,* Rosalin H. Arends, Ph.D.,† Danny D. Shen, Ph.D.,‡ Christopher M. Bernards, M.D.§
The Fate of Intrathecal Drugs

Rostral spread & Lipid Solubility

- Volume of Distribution
  - Hydrophobic: Greater Vd in SC
  - More rapid partitioning
    out of aqueous CSF
    to hydrophobic environments

- Different Clearance Rates
  of Drugs from CSF
  - Rates increase with lipophilicity
  - Supraspinal side - effects
Spinal Cord Dorsal Horn
Target for spinal opioids

- Opioids: Penetration into spinal cord
- **Target:** Gray matter
- Bioavailability of opioids at receptors
- Lipophilicity
  - Ability to reach gray matter
  - Accumulation in white matter
Morphine

Hydrophilic
Low SC Volume of distribution
Slow clearance into plasma
High normalized AUC of SC
High integral exposure of SC
Preferential distribution in gray matter

Other opioids

Low integral exposure of SC
Alfentanil: high clearance from SC
Fentanyl: Rapid distribution into epidural fat
Sufentanil: High SC volume of distribution
Preferential distribution in white matter

Ummenhofer WC et al.
Anesthesiology 2000; 92: 739 – 753
Epidural opioids

- **Hydrophilic**
  - slow onset
  - prolonged duration
  - Morphine
  - Hydromorphone

- **Lipophilic**
  - rapid onset
  - short duration
  - Meperidine
  - Fentanyl
  - Sufentanil
  - Oxymorphone
  - Butorphanol
  - Alfentanil

Limited action of hydrophobic opioids spinally
Epidural vs IV Sufentanil

- Similar rate of vascular absorption
- Similar duration of analgesia
  - Requires similar doses
- Similar degree of analgesia
- Side effects
  - Similar incidence
- Analgesia produced by epidural infusion=
  result of uptake into plasma
  redistribution to brain & peripheral receptors
  no action on SC
- **No clinical advantage** of epidural fentanyl infusion over IV infusion

Coda BA et al, Anesthesiology 1999; 90: 90 - 108
Analgesia produced by epidural infusion
result of uptake into plasma
redistribution to brain & peripheral receptors
no action on SC

Analgesia produced by epidural bolus
selective spinal mechanism

Short – lived spinally mediated mechanism

No clinical advantage of epidural fentanyl infusion over IV infusion

Ginosar Y et al, Anesth Analg 2003; 97: 1428 - 1438
Epidural vs IV Fentanyl in Labour

- Analgesia produced by epidural infusion
  spinal site of analgesia
- Analgesia produced by epidural bolus
  selective spinal mechanism
- Different response to epidural fentanyl in labour

  ➡️ Endogenous analgesic systems activated by labour
  Decrease the amount of exogenous analgesic necessary to produce analgesic effect

  ➡️ Elevated endogenous opioids in labour

  ➡️ Pregnancy: increased sensitivity to LA
  Needs of spinal opioid to produce analgesia in the presence of LA: less

D'Angelo R et al, Anesthesiology 1998; 88: 1519 - 1523
Epidural vs IM Morphine

- Absorption
  - Similar rate of vascular absorption

- Duration of analgesia
  - Longer for epidural, despite lower dose
  - Higher CSF morphine concentrations for epidural

- Degree of analgesia
  - Lower pain scores and less additional analgesics for epidural

- Side effects
  - Similar incidence
<table>
<thead>
<tr>
<th>Epidural</th>
<th>Intrathecal</th>
</tr>
</thead>
<tbody>
<tr>
<td>- lower bioavailability (2% for morphine)</td>
<td>- higher bioavailability</td>
</tr>
<tr>
<td>- membrane penetration</td>
<td>- more side effects (drowsiness)</td>
</tr>
<tr>
<td>- vascular uptake</td>
<td>- higher spinal concentrations</td>
</tr>
<tr>
<td>- extradural fat</td>
<td>- spinal actions</td>
</tr>
<tr>
<td>- less side effects</td>
<td>dose dependent, as high doses can achieve</td>
</tr>
<tr>
<td>- supraspinal and spinal actions</td>
<td>significant plasma concentrations</td>
</tr>
<tr>
<td>- more evident with lipophilic opioids</td>
<td></td>
</tr>
</tbody>
</table>
Local anesthetics

- Mechanism of action

Bind to Na⁺ channels causing a conduction blockade, by preventing Na⁺ from entering the cell
Local anesthetics

• Mechanism of action

Bind to Na\(^+\) channels causing a conduction blockade, by preventing Na\(^+\) from entering the cell
Cerebrospinal Fluid Bioavailability and Pharmacokinetics of Bupivacaine and Lidocaine after Intrathecal and Epidural Administrations in Rabbits Using Microdialysis

ROZENN CLEMENT, JEAN-MARC MALINOVSKY, PASCAL LE CORRE, GILLES DOLLO, FRANCOIS CHEVANNE, and ROGER LE VERGE

Spinal biopharmaceutics of bupivacaine and lidocaine by microdialysis after their simultaneous administration in rabbits

Rozenn Clément*, Jean-Marc Malinovsky, Pascal Le Corre, Gilles Dollo, Francois Chevanne, Roger Le Verge

Laboratoire de Pharmacie Galénique et Biopharmacie, Faculté des Sciences Pharmaceutiques et Biologiques, Université de Rennes 1, 35043 Rennes Cedex, France

Local Anaesthetics
Epidural and CSF Pharmacokinetics

- Intrathecal Bioavailability of
  - Lignocaine
  - Bupivacaine
  - Mixture
- Rabbit Model of spinal anaesthesia
- Microdialysis Technique
- Simultaneous Administration
- 12.3% bupivacaine, 17.9% lignocaine
- 5.5% and 17.7% respectively if separate administration
Slower & Lower systemic resorption of bupivacaine

Increases intrathecal bioavailability of bupivacaine

Cause: Vasoconstrictive effects of lignacaine
Spinal Disposition and Meningeal Permeability of Local Anesthetics

Rozenn Clément,¹ Jean-Marc Malinovsky,¹ Patrice Hildgen,² Gilles Dollo,¹ Jean Pierre Estèbe,¹ François Chevanne,¹ Roger Le Verge,¹ and Pascal Le Corre¹,³

Conclusions. The unexpected increase in CSF bioavailability with a decrease in absorption rate through meninges emphasizes the role of specific competitive clearance and distribution processes in the epidural space.
Effect of Epinephrine on IT Pharmacokinetics of Ropivacaine after Epidural Administration

- Sheep model
- Microdialysis Sampling
- ROpI Epidural, IT AUC (0 – 2h) Increased
  28%, 27% respectively
- No differences in Cmax, Tmax
- INCREASED BIOAVAILABILITY of Ropi

Estebe LP et al, Anesthesiology 2005; 103: A912
Intrathecal COX2 inhibitors

Reduce hypersensitivity

Oral Rofecoxib 50 mgr

CSF rofecoxib levels 15% of plasma levels

Repeating daily dose

Doubles AUC in CSF

Cerebrospinal Fluid and Spinal Cord Distribution of Baclofen and Bupivacaine during Slow Intrathecal Infusion in Pigs

Christopher M. Bernards, M.D.*

- Slow Continuous Infusion
- Intrathecally
- Baclofen + Bupivacaine
- $21 \, \mu l/h$ or $1000 \, \mu l/h$
- Microdialysis technique
- Catheter in posterior SC
- End of experiment: SC segments 8h after infusion
- Extremely limited spread of BUPI from the site of infusion
- 21 µl/h
- Extremely limited spread of BUPI from the site of infusion
- BUPI detectable 7 cm from point of administration
- Rapid fall in concentration from the peak
- Significantly higher C in posterior half of SC

Figure 5. Bupivacaine concentration in anterior and posterior spinal cord segments

Concentration measured after 8 h of 0.75% bupivacaine infusion at 21 µl per hour in 12 pigs (18–23 kg). The x-axis is the distance of the spinal cord segment from the point of bupivacaine infusion (C.M. Bernards, unpublished data).
1000 μl/h

**BUPIVACAINE**

- C on SC correspondingly higher
- Limited rostro – caudal distribution
- Marked anterior posterior gradients

**BACLOFEN**

- Differences in C as a function of distance
- No antero-posterior gradient

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Fig. 3. Average concentration of bupivacaine in samples from all eight dialysis probes in the 1,000-μl/h infusion group (A). Each probe is also designated by a letter in parentheses, and the letters after the probe location indicate which sampling sites were significantly different from that site. Error bars omitted for clarity. B shows the average bupivacaine concentration in spinal cord specimens from the same group. Bupivacaine concentration differed significantly between the anterior and posterior halves of the spinal cord and as a function of distance from the site of administration.
CSF: A very poorly mixed compartment

Rostro-caudal gradients for CSF constituents (albumin, glucose)

CSF: not well mixed compartment

Cardiac Systole: Rostro – to – Caudal Kinetic Energy to spinal CSF

Cardiac Diastole: Reverse of force gradient

Reverse direction in CSF motion

Cardiac Cycle: To – and – Fro CSF motion, no net movement

Very little circumferential CSF motion
Ziconotide

- New spinal drug
- Interruption of Ca++ dependent primary afferent transmission of pain signals in SC
- Intrathecally: Distribution in CSF
- Clearance 0.38 ml/min
- Corresponds to the rate of turnover of CSF
- Rapid degradation by proteolysis
- Negligible amounts in systemic circulation

DepoFoam™ Encapsulation

**DepoFoam™ Particle** (diameter: 15 microns)

- Encapsulation: creates depot
- Controlled release of agent in biophase
- Redistribution
- Diffusion Modifier Formulation
- Single Injection epidurally
- High Doses Released slowly
- Postop pain
- Reduced Cmax
- Maintained AUC

Reference: SkyePharma Website. DepoFoam™ overview.

Please see full Prescribing Information.
Spinal Drug Administration

- **Does not guarantee** spinal site of action
- Spinal bioavailability of hydrophilic vs lipophilic: **superior**
- Lipid – soluble opioids administered by epidural infusion analgesia **not** by spinal mechanism
- **Intrathecally** lipid – soluble opioids spinal site of action rapid plasma clearance brainstem redistribution

**SPINAL SPACE:** Not pharmacokinetically homogenous

**EXTAPOLATION FROM PIGS TO HUMAN:** Far from certain

**FUTURE OF INTRATHECAL PHARMACOKINETICS**

Location, Location, Location
Explore Pharmacology