Comparison of pharmacokinetics and efficacy of oral and injectable medicine
Outline

• Background
• Results
  – Antibiotics
  – Non steroidal anti-inflammatory drugs (NSAIDs)
  – Vitamins
• Conclusions and recommendations
Outline

• Background

• Results
  – Antibiotics
  – Non steroidal anti-inflammatory drugs (NSAIDs)
  – Vitamins

• Conclusions and recommendations
Injections given with sterile and reused equipment worldwide

Regions:
- South America (lower mortality)
- Central Europe
- South America (higher mortality)
- West Africa
- East and Southern Africa
- South East Asia
- China and Pacific
- Eastern Europe and Central Asia
- South Asia
- Middle East Crescent

Legend:
- Injections given with non-sterile equipment
- Injections given with sterile equipment

Number of injections per person and per year
Injections: A dangerous engine of disease

- **Hepatitis B**
  - Highly infectious virus
  - Highest number of infections (21 million annually)
  - 32% of HBV infections

- **Hepatitis C**
  - More than 2 million infections each year
  - More than 40% of HCV infections

- **HIV**
  - More than 260 000 infections
  - Approximately 5% of HIV infections
Reported common conditions leading to injection prescription

- Infections
  - Fever
  - Upper Respiratory Infection/ Ear Infection
  - Pneumonia
  - Tonsillitis
  - Pelvic Inflammatory Disease
  - Skin Infections
  - Diarrhea
  - Urinary tract infection
- Asthma
- Other
  - Malaise
  - Fatigue
  - Old Age

Simonsen et al. WHO 1999
Reported injectable medicines commonly used

- Antibiotics
- Anti-inflammatory agents / Analgesics
- Vitamins

Simonsen et al. WHO 1999
Reported factors leading to injection overuse

- Prescriber-associated factors
  - Perceptions regarding injections
  - Assumptions about patient’s expectations

- Patient-associated factors
  - Perceptions regarding injections
  - Therapeutic expectation

- System issues
  - Lack of effective oral medications
  - Financial implications

Reeler et. al. WHO 2000
Reported prescribers’ reasons for the use of injections

- Pharmacokinetics
  - “Strength” of injectables
  - Rapid onset of action
  - Poor intestinal absorption of oral medications
  - Absence of effective oral medications

- Other
  - Recommendations by Professors/Ministry of Health
  - Direct observed therapy

- Patient care issues
  - Inability of patient to take medications by mouth
  - Patient’s desire for injection
  - Chronic condition of patient (illness, malnutrition or alcohol abuse)
Misconceptions about injections among prescribers

- Oral absorption is variable, whereas parenteral administration assures high drug levels
- Injectable drugs are “stronger” than oral drugs
- Injectable drugs have more rapid onset of action
- Chronic conditions (malnutrition) of patients leads to poor oral absorption of drugs
Misunderstanding between patients and prescribers leading to injection overuse

5-20% of patients prefer injections

Providers' perception that patients prefer injections

Patients' perception that providers prefer injections

80-95% of patients do not prefer injections

Providers
Addressing Cognitive Dissonance Using Patient-Provider Interactional Group Discussions, Indonesia, 1993

Source: Long-term impact of small group interventions, Santoso et al., 1996
Objectives of the Study

• Primary objective
  – Provide an evidence base for decision making in prescribing injections

• Secondary objective
  – Compare pharmacokinetics of oral and injectable drugs
  – Describe the impact of malnutrition on drug pharmacokinetics
  – Compare the effectiveness of oral and injectable drugs in randomized clinical trials
  – Compare the cost of oral and injectable drugs
Literature review methods

- Medline
- Cochrane reviews
- Pharmacology textbook reviews
- Micromedex
Outline

- Background
- Results
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  - Non steroidal anti-inflammatory drugs (NSAIDs)
  - Vitamins
- Conclusions and recommendations
Parameters commonly used in pharmacokinetics

- Parameters affected by mode of administration
  - Absorption
  - Bio-availability
  - Peak serum concentration
  - Time to peak serum concentration

- Parameters unaffected by mode of administration
  - Half-life
  - Clearance
  - Distribution
  - Metabolism
  - Protein binding
Factors influencing absorption and bioavailability of medications

- Oral route
  - Food consumption
  - Cation interaction
  - Gastric pH
  - Intrinsic absorptive capabilities of digestive tract
  - First pass hepatic metabolism

- IM route
  - Injection site
  - Diluent
  - Solubility of drug
  - Concentration of drug
  - Total surface area for diffusion
  - Blood flow to muscle injected

IV 100% bioavailable
Outline

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# Peak serum concentration of selected oral, IM and IV antibiotics

<table>
<thead>
<tr>
<th>Class of Antibiotic</th>
<th>Oral</th>
<th>IM</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural Penicillin</td>
<td>++</td>
<td>-</td>
<td>++++</td>
</tr>
<tr>
<td>Aminopenicillin</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>+</td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>+</td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td>Rifampin</td>
<td>+</td>
<td>NA</td>
<td>++</td>
</tr>
</tbody>
</table>

Source: Micromedex
Time to peak serum concentration by different modes of administration

- **Oral**
  - 30min – 6hrs

- **IM**
  - 30min – 3hrs*

- **IV**
  - End of infusion

* Natural penicillin time to peak serum concentration 4-24 hrs
Effect of malnutrition on the pharmacokinetics of antibiotics

- **Children**
  - Decreased clearance
  - Larger area under the curve
  - Potential toxicity

- **Adults**
  - Lower absorption (may be overcome by larger doses)
  - Increased clearance
  - Potential need for more frequent administration
### Injected and oral antibiotics in the treatment of mild to moderate infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of studies</th>
<th>Clinical outcome</th>
<th>Bacterial outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Studies reporting equivalence</td>
<td>Studies reporting parenteral benefit</td>
</tr>
<tr>
<td>Otitis media</td>
<td>4</td>
<td>4/4</td>
<td>0/4</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3</td>
<td>2/3</td>
<td>1/3*</td>
</tr>
<tr>
<td>STD</td>
<td>13</td>
<td>2/2</td>
<td>0/2</td>
</tr>
<tr>
<td>UTI</td>
<td>5</td>
<td>3/3</td>
<td>0/3</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>2</td>
<td>1/1</td>
<td>0/1</td>
</tr>
</tbody>
</table>

*Only in subset of study patients*
Sequential and prolonged parenteral antibiotics in the treatment of severe infections

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Bacterial outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Studies reporting equivalence</td>
</tr>
<tr>
<td>No. of studies</td>
<td>UTI</td>
</tr>
<tr>
<td></td>
<td>No. of studies</td>
</tr>
<tr>
<td></td>
<td>UTI</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2/2</td>
</tr>
<tr>
<td></td>
<td>0/2</td>
</tr>
<tr>
<td></td>
<td>1/2</td>
</tr>
<tr>
<td></td>
<td>0/2</td>
</tr>
</tbody>
</table>
### Compared cost of selected oral and parenteral antibiotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative cost of parenteral:oral per equivalent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>3:1</td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>4:1</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>5:1</td>
</tr>
</tbody>
</table>
Outline

• Background
• Results
  – Antibiotics
  – Non steroidal anti-inflammatory drugs (NSAIDs)
  – Vitamins
• Conclusions and recommendations
Comparison of the pharmacokinetics of different NSAIDs by route of administration

<table>
<thead>
<tr>
<th>Class</th>
<th>NSAID</th>
<th>Bioavailability (%)</th>
<th>Time to serum peak (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Oral</td>
<td>IM</td>
</tr>
<tr>
<td>Salicylic</td>
<td>Aspirin</td>
<td>80-100</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Lysine</td>
<td>---</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Acetylsalicylate</td>
<td>---</td>
<td>NA</td>
</tr>
<tr>
<td>Indolic</td>
<td>Indometacin</td>
<td>90-100</td>
<td>NA</td>
</tr>
<tr>
<td>Aryl-carboxylic</td>
<td>Ketoprofen</td>
<td>95-100</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
<td>80</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Diclofenac Na</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Ketorolac</td>
<td>80-100</td>
<td>100</td>
</tr>
<tr>
<td>Oxicam</td>
<td>Naproxen</td>
<td>100</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Piroxicam</td>
<td>100</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Isoxicam</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Fenamates</td>
<td>Meloxicam</td>
<td>89</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Niflumic ac.</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Pyrazolic</td>
<td>Phenylbutazone</td>
<td>100</td>
<td>---</td>
</tr>
</tbody>
</table>
## Randomized clinical trials comparing the outcome of oral and injectable NSAIDs in various clinical situations

<table>
<thead>
<tr>
<th>Authors</th>
<th>Diagnosis</th>
<th>Oral dosage and frequency</th>
<th>Injectable dosage and frequency</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comb</td>
<td>Rheumatoid arthritis</td>
<td>Meloxicam</td>
<td>Meloxicam IM</td>
<td>Both effective and well-tolerated</td>
</tr>
<tr>
<td>Auvinet</td>
<td>Acute Sciatica</td>
<td>Meloxicam</td>
<td>Meloxicam IM</td>
<td>Both effective</td>
</tr>
<tr>
<td>Turner</td>
<td>Pain after surgery</td>
<td>R. indometacin</td>
<td>Ketorolac IM</td>
<td>No significant difference in pain</td>
</tr>
<tr>
<td>Shresta</td>
<td>Acute gout</td>
<td>Indometacin</td>
<td>Ketorolac IM</td>
<td>Both similar in the relief</td>
</tr>
<tr>
<td>Kumara</td>
<td>Molar surgery</td>
<td>Tenoxicam</td>
<td>Tenoxicam IV</td>
<td>Both equally effective</td>
</tr>
<tr>
<td>Tuomilehto</td>
<td>Adenoidectomy</td>
<td>Ketoprofen</td>
<td>Ketoprofen</td>
<td>No differences in pain scores,</td>
</tr>
<tr>
<td>Supervia</td>
<td>Renal colic</td>
<td>Piroxicam, Diclofenac IM</td>
<td></td>
<td>No significant difference</td>
</tr>
<tr>
<td>Evans</td>
<td>Ductus arteriosus</td>
<td>Indometacin</td>
<td>Indometacin IV</td>
<td>Intravenous form superior</td>
</tr>
</tbody>
</table>
Outline

• Background
• Results
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• Conclusions and recommendations
Pharmacokinetics of selected vitamins

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Oral Administration</th>
<th>IM Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absorption</td>
<td>Time to peak serum conc.</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>Well</td>
<td>1.25hrs</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Well</td>
<td>8-12 hrs</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Well</td>
<td>6-12 hrs</td>
</tr>
</tbody>
</table>

Source: Micromedex
Compared outcomes of oral and IM administration for selected vitamins

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Number of Studies</th>
<th>Outcome Equal Oral and IM</th>
</tr>
</thead>
<tbody>
<tr>
<td>B6</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>B12</td>
<td>1</td>
<td>1/1 @</td>
</tr>
<tr>
<td>K</td>
<td>2</td>
<td>1 / 2 *</td>
</tr>
</tbody>
</table>

@ clinical outcome  *Markers of Vitamin K status
Outline

• Background
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Conclusions (1)

- There is minimal to no benefit of IM versus oral administration of drugs in terms of pharmacokinetics.
- IV administration results in shorter onset of action and for some drugs higher bioavailability and peak serum levels.
- The issue of onset of action is clinically relevant only in life threatening illness.
Conclusions (2)

- Normal drug dosing in malnourished children may lead to toxic drug levels.
- Undernourished adults may need drug dosing at the high end of the therapeutic range given more frequently.
- The pharmacokinetic advantage of parenteral over oral drugs does not translate to better clinical outcomes in mild-moderate illness.
- Even in serious illnesses, sequential therapy within 2-5 days can be as effective as prolonged parenteral courses.
Recommendations: indication for therapeutic injections

- Serious and life-threatening illness
- Inability to swallow
- Profuse vomiting
- Absence of effective oral agent
- Significantly altered absorption pattern
Avoid *unnecessary* injections

Wise doctors all agree it's safer to take medicine by mouth.