Which is the Better Analgesic in Infants and Children: Paracetamol or NSAID

Brian Anderson PhD, FANZCA, FCICM

Professor Anaesthesiology
University of Auckland
New Zealand
New Zealand: a land of sheep
4,000,000 people
40,000,000 sheep
My students in New Zealand
Which is better?

• Both good analgesics for mild to moderate pain
  – a ceiling effect of approximately 5/10
• Both have impressive safety records in children and infants
• NSAIDs are widely used for PDA
  – assessment of analgesia limited in neonates
• My preference
  – combination therapy in children
  – Paracetamol is first choice in neonates
  – Short term NSAIDs can be added cautiously if paracetamol alone is inadequate
Paracetamol or NSAIDs

• How do we gauge effectiveness?
• What comparative information about effectiveness do we have?
• Why are there so few studies?
• Are there differences between neonates and children?
• How does adverse effects profiles influence choice?
• What is the role of combination therapy?
How do we gauge effectiveness?

• **Comparative studies in PACU**
  - Other drugs, local anaesthetics, placebo

• **Number Needed To Treat (NNT)**
  - Cochrane initiatives

• **Morphine sparing postoperatively**

• Concentration – Response Curves
Comparative Studies
- Dose Equivalence

- Rectal diclofenac 1 mg/kg
- Oral ibuprofen 10 mg/kg
- Rectal paracetamol 40 mg/kg
- IV ketoprofen 5 mg/kg
- IV ketorolac 0.5 mg/kg

Comparative Studies

• Route of administration
• Age range subjects
• Timing of effect measure
• Type of pain insult
• Initial pain score
• Placebo effects
• Morphine as gold standard

• No concentrations
Number Needed To Treat (NNT)

- use a measure of at least 50% pain relief as a common descriptor of analgesic effectiveness
- e.g. NNT of 2.5 means that 2 of every 5 adult patients with pain of moderate to severe intensity will experience at least 50% pain relief, which they would not have had with placebo.

<table>
<thead>
<tr>
<th>Ibuprofen (mg)</th>
<th>NNT (95% CI)</th>
<th>Diclofenac (mg)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>4.7 (3.3-8)</td>
<td>25</td>
<td>2.6 (2.2-3.3)</td>
</tr>
<tr>
<td>100</td>
<td>4.3 (3.2-6.4)</td>
<td>50</td>
<td>2.7 (2.4-3)</td>
</tr>
<tr>
<td>200</td>
<td>2.7 (2.5–3)</td>
<td>100</td>
<td>2.3 (2-2.5)</td>
</tr>
<tr>
<td>400</td>
<td>2.5 (2.4-2.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>600</td>
<td>2.7 (2.0-4.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>800</td>
<td>1.6 (1.3–2.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Editorial

The placebo (I shall please) – is it so pleasing in children?

BRIAN ANDERSON PhD FANZCA FFICM* AND NOEL CRANSWICK Med Sc MBBS FRCA†

*Department of Anaesthesiology, University of Auckland, New Zealand and †Clinical Pharmacology and Australian Paediatric Pharmacology Research Unit, Royal Children’s Hospital and Murdoch Children’s Research Institute, Melbourne, Vic., Australia
Immediate Rescue Design
Morphine Sparing

Diclofenac 1 mg/kg 8 h ↓ 40 % PCA
Paracetamol 15 mg/kg 6 h ↓ 17 % PCA

Morton NS. Br J Anaesth 1999;82:715
Morphine Sparing Studies

**Primary surrogate measure**
- differences in cumulative rescue dosing between drug and placebo

**Secondary outcome measure**
- percent children requiring rescue medication
- time to rescue
- pain scores

**Concerns**
- Long acting opioids mask effect treatment
- Dose compromise between adverse and analgesic effects
- Drug interactions
- Drug onset times for analgesia

Berde CB. Pediatrics 2012
Forrest plot for NSAIDs as study drug
- negative scores favour drug over control

Papers=29
T&A dominant surgery

Total opioid dose (mg/kg/h)
best measure for NSAID trials

Kossowsky Anesthesiology 2015
Forrest plot for acetaminophen as study drug
- negative scores favour drug over control

Papers=11

Total opioid dose (mg/kg/h) best measure for ACET trials

Kossowsky Anesthesiology 2015
Paracetamol or NSAIDs

- How do we gauge effectiveness?
- **What comparative information about effectiveness do we have?**
- Why are there so few studies?
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- What is the role of combination therapy?
What Information Do We Have?

The Concentration-Response Relationship

NOT

The Dose-Response Relationship
Clinical Pharmacology

Pharmacokinetics

\[ C = \frac{Dose}{V} \cdot e^{-\frac{CL}{V} \cdot t} \]

Pharmacodynamics

\[ Effect = \frac{E_{\text{max}} \cdot C^N}{EC_{50}^N + C^N} \]

Holford 2009
The Sigmoid Emax Model

- Maximum response
- $\frac{1}{2} \text{Emax}$
- $E_{50} = 8$
- $E_0 = 2$
- $N = 0.3$
- $N = 1$
- $N = 3$
- $N = 10$
### Some Typical Emax Models

<table>
<thead>
<tr>
<th></th>
<th>Paracetamol</th>
<th>Ibuprofen</th>
<th>Ketorolac</th>
<th>Diclofenac</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Emax (0-10)</strong></td>
<td>5.2</td>
<td>5.1</td>
<td>8.5</td>
<td>4.89</td>
</tr>
<tr>
<td><strong>EC50</strong></td>
<td>9.8 mg/L</td>
<td>10.2 mg/L</td>
<td>0.37 mg/L</td>
<td>1.2 mg/L</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>T1/2keo</strong></td>
<td>53 min</td>
<td>28 min</td>
<td>24 min</td>
<td>14 min</td>
</tr>
</tbody>
</table>
Paracetamol or NSAIDs

• How do we gauge effectiveness?
• What comparative information about effectiveness do we have?
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• What is the role of combination therapy?
Problems on the road getting there
Problems on the road getting there: New Zealand
Problems Interpreting Simple Analgesics in Children

- Size and Age
- Administration route and dose
- Delayed Effects
- Pain score used
- Pain type
- Initial pain score
- Discrete vs. continuous data
- Interactions & stereoisomers
- Placebo effects
- Disease progression
- Drop outs
Confusion with route, dose, formulation etc

Dose Equivalence

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CONCENTRATION IS THE LINK
Formulation time-concentration profile

Van der Marel C. Paediatr Anaesth 2004;14:443-51
Ibuprofen Stereoselectivity

- R(+) & S(-) stereoisomers
- S(-) active
- clearance $S(-) = 2.5 \times$ clearance $R(+) $
- $V_{d\ S(-)} \neq V_{d\ R(+) }$
  - PK predictions based on racemic assays overestimate duration effect

Gregoire N. J Clin Pharmacol 2004;44:1114
Active Metabolites

- Morphine – M6G
- Tramadol – M1 metabolite
- Ketamine – norketamine
- Diclofenac – hydroxy metabolite
FIGURE 1
GENETICS OF CYP 2D6 METABOLIZING EFFECTS ON NORTRIPTYLINE

CYP = cytochrome P450; MR = metabolic ratio of parent debrisoquine ÷ metabolic OH-debrisoquine.

Contributors to analgesic variability

- Nongenetic factors with genetic links:
  - Physiological (Age, sex)
  - Drug interactions
  - Ethnicity/race
  - Psychological (anxiety, stress)

- Genetic factors:
  - Metabolizing enzymes: CYP2D6, UGT2B7
  - Transporters: ABCB1
  - Opioid receptors: OPRM1, COMT, MC1R
  - Signal transduction

Source: Pharmacogenomics © 2012 Future Medicine Ltd
Paracetamol or NSAIDs

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Pharmacokinetics

What the body does to the drug

The most important PK parameter is CLEARANCE

This determines maintenance dosing

**DOSE = CL x Target Concentration**
The Major PK Covariates in Children

- SIZE
- AGE
- Organ Function
- Body Composition
- Drug interactions
- Pharmacogenetics
- Environmental factors
- Circadian rhythms

What the body does to the drug
Allometry alone fails under 10 kg for propofol

Solid line: \( CL = 0.071 \times BW^{0.78} \)
Dashed line: \( CL = 1.44 \times \left( \frac{BW}{70} \right)^{0.75} \)
Impact of Sex

- Behavioural differences pain response
- P-glycoprotein expression, CYP3A4
- Renal Function (Cockcroft and Gault)
  - Cockcroft DW. Nephron 16:31-41
Pharmacodynamics

What the drug does to the body

The important PD parameters are $E_{\text{max}}$ and $E_{\text{C50}}$

$$Effect = \frac{E_{\text{max}} \cdot \text{conc}^N}{E_{\text{C50}}^N + \text{conc}^N}$$
Explore concentration range

- Pain Score
- Effect compartment concentration (mg/L)
- Ibuprofen
- Acetaminophen
Onset time of analgesia ($T_{1/2}\text{Keo}$)

Ibuprofen $T_{1/2}\text{keo} = 28$ min
Paracetamol $T_{1/2}\text{keo} = 50$ min
$T_{1/2}\text{keo}$ smaller with smaller size
Pain Score

- Pain type
  - Acute, recurrent, chronic
- Pain source
  - Bone, renal respond to NSAIDs
- What is score for satisfactory pain relief
- Pain scores not linear weighting
- Neonate vs child
  - Scoring system, pain type
- What is meaningful reduction (e.g. 30%)
- Initial pain score e.g. 4/10 and inadequacies
  - Malviya, Voepel-Lewis Pediatr Anesth 2014;24:454
More Tricky Aspects in Kids

- Placebo/Nocebo effects
- Disease progression
- Drop outs
Placebo Response

Anderson BJ. Eur J Clin Pharmacol 2001; 57: 559

Fig. 8 The time course of pain resolution (disease progression) after hospital discharge in children under 10 years (open triangles) and over 10 years (open squares). Data taken from Lavy [1]
Impact of a drop out model
NEW CUYAMAMA

Population 562
Ft above sea level 2150
Established 1951
TOTAL 4663
Differences between neonate and child

• Poorly explored
  – $T_{1/2}$ shorter
  – Pain type, scoring system

• Placebo/nocebo effects greater in children than adults

• May not be huge differences
  – Paracetamol target 10 mg/L in neonates and children
    • Allegaert K. Pediatr Anesth 2013; 23:45-50
    • Anderson BJ. Eur J Clin Pharmacol 2001; 57: 559-569
**Paracetamol or NSAIDs**

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- **How does adverse effects profiles influence choice?**
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What dose is best for clinical use?
Is there any added benefit of going higher than 100 mg?
Paracetamol hepatotoxicity in children - chronic dosing

- Toxicity > 150 mg/kg (3-8 days)

- > 90 mg/kg/day in infants

- > 75 mg/kg/day in children
  - Rivera-Penera et al. J Pediatr 1997; 130: 300-4

- Neonatal protection?
  - Reduced CYP2E1 activity
**NSAIDs Adverse Effects**

**Concerns in children**

The increasing use of NSAIDs has lead to increased reporting of adverse effects. The ubiquitous nature of prostaglandin influence in the body renders a ubiquitous adverse effect profile.

Common areas of concern in children include:

- Renal function
- Postoperative coagulation
- Gastrointestinal function
- Bone healing
- Exacerbation of asthma
- Cardiovascular risk (adults)

Hopes that COX-2 selective inhibitors may have a reduced adverse effect profile have not really eventuated.

Great shoes are not always suitable in rough terrain. Great drugs can have adverse effects in some circumstances.
Adverse gastrointestinal effects are significant in adults, particularly in those with peptic ulcer disease, H pylori or advanced age.

The risk of acute GI bleeding in children given short-term ibuprofen was estimated to be 7.2/100,000 (CI 2-18/100,000) and was not different from those children given paracetamol (Lesko, 1985).

The incidence of clinically significant gastropathy is comparable to adults in children given NSAIDs for juvenile rheumatoid arthritis, but gastro-duodenal injury may be very much higher (75 %) depending on assessment criteria (e.g. abdominal pain, anaemia, endoscopy).

Data for neonates are not available.

The upper GI tract. Commonly reported gastrointestinal symptoms in children given NSAIDs include abdominal pain, nausea, vomiting and diarrhoea.
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• **What is the role of combination therapy?**
Combination Therapy
- Theoretical reasons

- Mechanism of action different
- Pain type specificity
- Adverse effect profiles are dose related
- Different absorption profiles
- Different durations of action
- PD profiles and where common doses sit on profile
- Teq ($T_{1/2}\text{keo}$) differ; 60 min vs. 20-30 min
- Interactions e.g. possible altered absorption effects
- Cost/benefit ratios
- Placebo effects
A Single-Tablet Fixed-Dose Combination of Racemic Ibuprofen/Paracetamol in the Management of Moderate to Severe Postoperative Dental Pain in Adult and Adolescent Patients: A Multicenter, Two-Stage, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Factorial Study

Donald R. Mehlsch, MD, DDS; Sue Aspley, PhD; Stephen E. Daniels, DO; Kristin A. Southerden, MS; and Kyle S. Christensen, DDS

1D.R. Mehlsch & Associates, Palm Desert, California; 2Reckitt Benckiser Healthcare Ltd., Hull, United Kingdom; 3Premier Research Group, Austin, Texas; and 4Premier Research Group, Salt Lake City, Utah
Paracetamol-Diclofenac Relationship

Hannam J. Pediatr Anesth 2014
What dose combination?
Which is better?

• Both good analgesics for mild to moderate pain
  – a ceiling effect of approximately 5/10
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THE END
Predictions Match Observations
18 Orders of Magnitude

Fractal Geometry

Clearance changes with weight

\[ Y = a \times Weight^{b} \]
The Link Parameter

Elimination half-time
\( T_{1/2}^{\text{keo}} = \frac{\ln(2)}{\text{K}_{\text{eo}}} \)

\[ \text{Dose} \xrightarrow{\text{F}} \text{Ka, Tlag} \]

\[ \text{Vd} \xrightarrow{\text{K}_{\text{eo}}} \text{Cp} \]

\[ \text{CL} \]

\[ \text{Ve} \xrightarrow{\text{C}_{\text{e}}} \text{Effect} \]

\[ \text{Effect} = \frac{E_{\text{max}} \cdot C_{N}}{E C_{50}^{N} + C_{N}} \]
Delayed Effects

Figure 3  (A) Effect compartment–response relationship for paracetamol analgesia after tonsillectomy. Pharmacodynamic parameter estimates used were $E_{\text{max}} = 5.17$ and $E_{\text{50}} = 9.98$ mg/l. The Hill coefficient ($N$) was 1. 0 is the worst pain possible on a visual analogue scale (VAS) of 0–10. Parameter estimates taken from Anderson et al.\textsuperscript{11} (B) The relationship between the plasma concentration and analgesic effect shows clockwise hysteresis. The equilibration half-time ($T_{\text{eq}}$) of the analgesic effect compartment was 53 min. Parameter estimates taken from Anderson et al.\textsuperscript{11} (C) Temporal relationships for plasma concentration, effect compartment concentration and analgesic effect after administration of 12.5 mg/kg paracetamol elixir to a child. The absorption half-time used was 4.5 min. Parameter estimates taken from Anderson et al.\textsuperscript{11}

Anderson BJ. Arch Dis Child 2008
Simple Impact of Another Drug

![Graph showing pain score vs. effect compartment concentration. The graph compares two curves, one with EC50 = 7 and another with EC50 = 10. The x-axis represents effect compartment concentration in mg/L, ranging from 0 to 20. The y-axis represents pain score on a Visual Analog Scale (VAS) from 0 to 10.]
Isobolograph of dose or concentration pairs for two drugs (drug A and drug B) that together cause a single level of effect. A) Line of additivity (or no interaction). The effect is equal for all parts of the line. B) infra-additivity where drug doses required for the effect are greater than expected. C) Supra-additivity, where the drug doses required for the effect are smaller than expected.
The Surface Response

Isobolograph only shows part of the story
Acetaminophen/Ibuprofen

Hannan J. Pediatr Anaesth 2011
Simulation 5 y 20 kg
Isoboles of concentration pairs that together cause a 1 cm, 2 cm, 3 cm and 4 cm reduction in pain from baseline (VAS 0-10). Ce is the concentration in the effect site compartment. A 2 cm reduction in pain score can be achieved with Ce paracetamol 11.75 mg.l⁻¹, or Ce diclofenac 1.07 mg.l⁻¹. Alternatively this Ce of paracetamol may be halved to 5.88 mg.l⁻¹, and combined with 0.54 mg.l⁻¹ of diclofenac to achieve the same effect.

Hannam J. Pediatr Anesth 2014
Confusion with route, dose, formulation etc

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• Rectal paracetamol 40 mg/kg
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CONCENTRATION IS THE LINK
M6G - An active metabolite

\[
\text{Effect} = E_0 - (E_0 - E_{\text{MAX}}) \cdot \frac{\text{CONC}^H}{\text{CONC}^H + \text{EC}_{50}^H}
\]

\[
\text{Effect}_{\text{total}} = E_M + E_{M6G}
\]

T1/2keo for morphine = 16 min

T1/2keo for M6G = 6.7 h