Innovative trial designs including Bayesian approaches

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Learning Points

• Dose is based on PK, PD and adverse effects
• Variability affects response to medicines
• Major sources of usual variability are maturation, size, drug interactions and genes
• Modelling and simulation, using Bayesian approaches, can be used to predict dose, demonstrate effect and inform future studies
New Zealand: a land of sheep
4,000,000 people
40,000,000 sheep
The Students in NZ
Assumptions

- Basic understanding of population modelling
  - Underlying theme is variability and prior knowledge (Bayesian)
  - Amy Cheung - PKPD
- Aware difficulties of study in children < 2 years
Population Approach

Describing the Signal and the Noise

... and it is the noise (variability) that is important

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

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

Anderson BJ. EJCP 2001
Mixed Effects Modelling

Fixed Effects (predictable variability)
- Covariates and parameters
- e.g. renal function and clearance

Random Effects (unpredictable variability)
- Parameter variability e.g. in clearance
- Residual error e.g. measurement error, process noise, model misspecification, assay error, transcription

Minimisation successful
Bourne D. mathematical modeling of PK data 1995
Population Modeling – a logical processor
Clinical trial designs and models for analgesic medications for acute pain in neonates, infants, toddlers, children, and adolescents: ACTTION recommendations


Pediatric Analgesic Clinical Trial Designs, Measures, and Extrapolation: Report of an FDA Scientific Workshop

Delivering transformative action in paediatric pain: a Lancet Child & Adolescent Health Commission

AUTHORS: Charles B. Berde, MD, PhD, Gary A. Walco, MD, MD, Elliot J. Knane, MD, K. J. S. Anand, MBBS, DPhil, Jacob V. Andrus, MD, PhD, Kenneth D. Craig, PhD, Carlton D. Dampier, MD, CPI, Julia C. Finkel, MD, Martin Gradua, MD, Cathie Johnson, RN, PhD, John Lanto, MD, Alyssa Lebel, MD, Lynne G. Maxwell, MD, Patrick McGinnis, DC, PhD, Timothy F. Oberlander, MD, Laura E. Schanberg, MD, Bonnie Stevens, RN, PhD, Anna Tedjo, BSPhm, MSc, PhD, Cyll L. von Baeyer, PhD, Myron Yaster, MD, and William T. Zempolski, MD
The intellectual health of clinical drug evaluation

Lewis B. Sheiner, MD San Francisco, Calif.

"We have to trust the scientific judgement of the scientists... Statistics should be their handmaiden, not their jailer."

—D. Salzburg

Let me introduce my topic by presenting three symptomatic examples of an intellectual illness from which I believe clinical research in general, and drug trials in particular, is suffering.

1. An irrelevant analysis. Fig. 1 is redrawn from a recent article in our Society's journal, Clinical Pharmacology & Therapeutics. The error bars are drawn on only one point on each curve, but these are typical of the rest of the points. The figure shows a characteristic time course of drug action, independent of dose, and a clear progression of pain relief as the dose of bromfenac increases. Rather than stressing this compatibility with expectation and rather than deriving a dose-response curve from which the (time course of) response to any dose could be predicted, why do the authors confine themselves to pairwise comparisons of the mean (over time) response between doses and deem it relevant to tell us, for example, that "No significant distinction was achieved between the 10 and 25 mg bromfenac doses"?2

2. A great waste. It seems that Smith Kline & French Laboratories (Philadelphia, Pa.) studied about surely many tens, if not hundreds, of millions of dollars. Although proving unequivocally that the drug was effective, all those studies apparently did not reveal the minimum effective dose. This is not just an isolated instance. Temple3 has pointed out that for many drugs the dose approved initially is considerably greater than that ultimately found to be adequate. This has been true, for example, for many β-blockers and more recently for zidovudine.

3. An excessive conservatism. Imagine a double-blind crossover placebo-controlled study of a new drug for the prophylaxis of angina. Fig. 2 shows both the placebo and active drug data on one hypothetical patient. Here the intended dose of the new drug was one per day, and if the patient had taken the new drug as intended, there would be no reason to think it was superior to placebo on the basis of the similar frequency of anginal attacks on both treatments.

But what if a medication monitor had been used,4 and the pattern of dosage was the one listed as Actual in Fig. 2? It seems the patient did not take any drug at all for the first 2 days and had anginal attacks on days 2 and 3. He then took the drug for 3 days without angina, stopped taking the drug, and had an attack the next day. The same thing happened again after 1 week of full compliance without angina. Surely, if there were multiple records like this one and the placebo records did not show similar patterns, we would be
An approach around these difficulties

What do anaesthesiologists do?
Clinical Pharmacology

**Pharmacokinetics**

- CL
- V

**Pharmacodynamics**

- Emax
- EC$_{50}$

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**Concentration**

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

**Effect**

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

Holford 2009
Example: What dose propofol in infants

- PKPD parameters incorporated into pump
ANAESTHESIA IS NOT...

the half-asleep watching the half-wake being half-murdered by the half-witted

Malcolm Fisher
**Emax Model Upside Down**

**Effect**

\[ \text{Effect} = E0 + \frac{E_{MAX} \times C^N}{(C_{50}^N + C.e^N)} \]

**Bispectral Index**

\[ \text{Bispectral Index} = BIS_0 - \frac{E_{MAX} \times C^N}{(C_{50}^N + C.e^N)} \]

Most Drugs

- Maximum response
- \( \frac{1}{2} \) Emax
- \( EC_{50} = 8 \)
- \( E0 = 2 \)

Bispectral Index

- \( C_{50} = 5 \)
- \( E_{MAX} = 90 \)
- \( N = 0.3, 1, 3, 10 \)
### Target Concentration (PD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>95%CI</th>
<th>Sh %</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIS₀</td>
<td>94</td>
<td>86.8, 94.6</td>
<td>48.1</td>
<td>5</td>
</tr>
<tr>
<td>E_max</td>
<td>0.81</td>
<td>0.70, 0.93</td>
<td>47.8</td>
<td>14.8</td>
</tr>
<tr>
<td>C₅₀,PROP (mg/L)</td>
<td>2.99</td>
<td>2.45, 3.66</td>
<td>47.1</td>
<td>35.4</td>
</tr>
<tr>
<td>T₁/₂keo,PROP (min)</td>
<td>2.38</td>
<td>4.21, 14.6</td>
<td>45.9</td>
<td>67.6</td>
</tr>
<tr>
<td>Hill</td>
<td>1.55</td>
<td>1.31, 2.37</td>
<td>44.6</td>
<td>44.5</td>
</tr>
<tr>
<td>Additive residual Error (BIS units)</td>
<td>5.9</td>
<td>5.1, 6.8</td>
<td>-</td>
<td>η₉₀ 0.363</td>
</tr>
</tbody>
</table>

Target Effect BIS=50
Target concentration 3 mg/L

Fuentes Pediatric Anesth 2018
# Propofol Clearance Variability (PK)

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>95%CI</th>
<th>Sh %</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>V1 (L/70 kg)</strong></td>
<td>18.5</td>
<td>5.2, 23.8</td>
<td>8.5</td>
<td>41.1</td>
</tr>
<tr>
<td><strong>V2 (L/70 kg)</strong></td>
<td>41.1</td>
<td>29.2, 58.1</td>
<td>9.7</td>
<td>23.3</td>
</tr>
<tr>
<td><strong>V3 (L/70 kg)</strong></td>
<td>230</td>
<td>178, 390</td>
<td>14.5</td>
<td>50.3</td>
</tr>
<tr>
<td><strong>CL (L/min/70 kg)</strong></td>
<td>1.93</td>
<td>1.74, 2.19</td>
<td>2.9</td>
<td>40.7</td>
</tr>
<tr>
<td><strong>Q2 (L/min/70 kg)</strong></td>
<td>3.82</td>
<td>3.24, 7.64</td>
<td>11.1</td>
<td>47.4</td>
</tr>
<tr>
<td><strong>Q3 (L/min/70 kg)</strong></td>
<td>0.837</td>
<td>1.09, 1.65</td>
<td>6.2</td>
<td>69.6</td>
</tr>
<tr>
<td><strong>TM50</strong></td>
<td>42.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Hill</strong></td>
<td>5.88</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Additive residual Error (µg.mL⁻¹)</td>
<td>0.012</td>
<td>0.0002, 0.0184</td>
<td>η_RUV 0.56</td>
<td></td>
</tr>
<tr>
<td>Proportional Residual Error (%)</td>
<td>16.9</td>
<td>12.5, 28.3</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\[ MF = \frac{PMA^{Hill}}{TM^{Hill}} + PMA^{Hill} \]

\[ CL_{GRP} = CL_{STD} \cdot \left(\frac{WT}{WT_{STD}}\right)^{3/4} \cdot MF \]

Morse J. Pediatric Anesth 2019
# Propofol Dosing Regimen

<table>
<thead>
<tr>
<th>Age</th>
<th>Induction dose (mg/kg)</th>
<th>0-15 min</th>
<th>15-30 min</th>
<th>30-60 min</th>
<th>60 – 120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>27-44 PMA weeks</td>
<td>2</td>
<td>9</td>
<td>7</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>44-52 PMA weeks</td>
<td>2.5</td>
<td>11</td>
<td>10</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>3-12 months</td>
<td>2.5</td>
<td>12</td>
<td>11</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>1-3 years</td>
<td>2.5</td>
<td>13</td>
<td>12</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

Target plasma concentration 3 µg.mL⁻¹

Morse J. Pediatr Anesth 2019
Simulation of 1000 individuals reveals unexplained variability.

Half of the predictions were in the range 80-125% of the target concentration between 5 and 90 minutes of infusion duration.

Anderson BJ. Pediatr Anesth 2019
**Target Concentration Strategy**

Choose the target effect (e.g., magnitude of pain reduction sought)

Use $E_{\text{MAX}}$ and $C_{50}$ to predict the target concentration (i.e., the plasma concentration of drug that will achieve the sought pain reduction)

Predict:
- Loading dose = target concentration $\times V$
- Maintenance dose or infusion rate = target concentration $\times CL$

Revise $V$ and CL

Measure response (e.g., pain score)

Measure concentrations

Revise target concentration

---

*Figure 6: Strategy to determine the correct dose of pharmacological treatment*

$C_{50} =$ concentration at 50% of maximum response. $CL =$ clearance. $E_{\text{MAX}} =$ maximum effect. $V =$ volume of distribution.

Eccleston C The Lancet Child and Adolescent Health Commission 2021
Application of principles to Opioids: Example, Diamorphine (Heroin) age < 2 years

• Use restricted to a few countries
• Paediatric dose acute and palliative care unknown
• Renewed interest in the drug, clinical trials advocated
• Metabolism complex, never described in children (PK)
  – Maturation
  – Size
  – Physiological functions (renal system clears some metabolites)
• Effect attributed to metabolite, morphine (PD)
  – Other metabolites also have effect
  – No concentration-response relationship for morphine
  – Drug interactions
  – Pharmacogenomics
Diamorphine Metabolism

- **Oral Diamorphine**
  - $T_{\text{ABS}} \text{ oral}$
  - $F_{D\text{IAMORPH}} \text{ oral}$

- **Oral Morphine**
  - $T_{\text{ABS}} \text{ oral}$
  - $F_{M\text{ORP}} \text{ oral} = 0.3$

- **Conversion** Diamorphine to Morphine

- **Intranasal Diamorphine**
  - $T_{\text{ABS}} \text{ IN}$
  - $F_{D\text{IAMORPH}} \text{ IN}$

- **Morphine**
  - $T_{1/2} k_{\text{DIA}}$
  - $T_{1/2} k_{\text{MAM}}$

- **6-monooacetylemophine**

- **3-monooacetylemophine**

- **M3G**

- **M6G**

- **Effect Compartment**

- **IV**
  - $F_{\text{IV}} = 1$
Diamorphine Pharmacokinetics

- Adult rate constants known
- Pediatric morphine PK described
- Formulation bioavailability assumed
- PK maturation models known (premature neonate to adult)
  - Premature neonatal data (Barrett 1991-6, ventilation)
- Renal function maturation known
- Size factors assumed (allometry)
- PBPK modelling supportive
Diamorphine Metabolism

**Oral Diamorphine**
- $T_{ABS}$ oral = 40 min
- $F_{DIAM}$ oral = 0.23

**Oral Morphine**
- $T_{ABS}$ oral = 40 min
- $F_{MORP}$ oral = 0.3

**Diamorphine** $V_{DIAM}$ 58.8 L
- $F_{IV}$ = 1
- $T_{ABS}$ IN = 10 min
- $F_{DIAM}$ IN = 0.5
- $k_{DIA}$ = 11/h
- Conversion Factor $D_{DIAM}$ $M_{MORP}$ = 2

**Morphine** $V_{MOR}$ 136 L
- $CL_{M3G}$ 64.3 L/h
- $F_{VENT}$ 0.74
- $CL_{M6G}$ 3.63 L/h
- $F_{VENT}$ 0.74
- Poorly absorbed

6-monoo-acetylmorphine $V_{6-MAM}$ 58.8 L
- $T_{1/2}ke_{MORP}$ = 16 min
- $T_{1/2}ke_{M6G}$ = 6.7 h
- $T_{1/2}ke_{6-MAM}$ = 1 min

**Effect Compartment**

Intranasal Diamorphine

M3G $V_{M3G}$ 23 L
- $CL_{M3G}$ 17.4 L/h

M6G $V_{M6G}$ 30 L
- $CL_{M6G}$ 5.8 L/h
Diamorphine Pharmacodynamics

- Link parameters known ($T_{1/2\text{keo}}$)
- No Concentration-response
  - unlike NSAIDs, tramadol, acetaminophen
- Maturation receptors poorly defined
- Metabolite interactions (6-MAM, M6G)

BUT

Target concentration defined

- morphine 10 mcg/L
- respiratory concentration-response same neonates-adults

Hannam JA, Pediatr Anesth 2018
Anderson BJ. Pediatr Anesth 2019
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**Figure 6: Strategy to determine the correct dose of pharmacological treatment**

\( C_{50} \) = concentration at 50% of maximum response. \( CL \) = clearance. \( E_{\text{MAX}} \) = maximum effect. \( V \) = volume of distribution.

Eccleston C The Lancet Child and Adolescent Health Commission 2021
Population Modelling

Quantify the exposure-response relationship

Provide clarity and insight

Enable extrapolation beyond the observed data

Provide scientific rationale to dose selection

A knowledge management tool to capture and integrate pooled data from studies

Drive decision making during drug development

Hypothesis generating – the learning phase of drug development

Give a mechanistic understanding of the drug effect - theory enrichment

Morse J. Curr Opin Anaesthesiology 2019
COMMENTARY

Learning versus confirming in clinical drug development

Lewis B. Sheiner, MD  San Francisco, Calif.
Drug Interactions: surface responses

Minto CF. Anesthesiology 2000; 92:1603-16
Opioid Drug Interactions

• Opioid drug interactions well described with anaesthesia agents
  – e.g., propofol-remifentanil

• Simple analgesic interactions in older children described
  – e.g., Hannam JA, Anderson BJ, Potts A. Acetaminophen, ibuprofen and tramadol analgesic interactions after adenotonsillectomy. Pediatr Anesth 2018; 28: 841-851
**FIGURE 1**

**GENETICS OF CYP 2D6 METABOLIZING EFFECTS ON NORTRIPTYLINE**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Ultrapid metabolizers</th>
<th>Extensive metabolizers</th>
<th>Intermediate metabolizers</th>
<th>Poor metabolizers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype</td>
<td>5%-10%</td>
<td>80%-65%</td>
<td>10%-15%</td>
<td>5%-10%</td>
</tr>
<tr>
<td>Frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Caucasian)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Graph showing distribution of nortriptyline dose requirement](image)

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

Impact of CYP2D6 on Tramadol Clearance

Contributors to analgesic variability

- Drug interactions
- Ethnicity/race
- Psychological (anxiety, stress)

Nongenetic factors with genetic links:
- Physiological (Age, sex)

Opioid analgesia and side effects

Pharmacokinetics (volume of distribution, clearance):
- Metabolizing enzymes (CYP2D6, UGT2B7)
- Transporters (ABCB1)

Pharmacodynamics (pain sensitivity, efficacy):
- Opioid receptors (OPRM1, COMT, MC1R)
- Signal transduction

Genetic factors
The intellectual health of clinical drug evaluation

Lewis B. Sheiner, MD San Francisco, Calif.

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—D. Salsburg

Clin Pharm Ther 1991

surely many tens, if not hundreds, of millions of dollars. Although proving unequivocally that the drug was effective, all those studies apparently did not reveal the minimum effective dose. This is not just an isolated in-
THE END