Clinical Measurement of Drug Action

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The $1,000,000 Questions

- Is this drug effective?
  - is it better than a competitor/alternative?

- Is this drug safe?
  - or at least is it reasonably well-tolerated?

What has to be measured to answer these questions?

Phases of Drug Development

- Phase 0
  - Predictions for Humans
- Phase 1
  - Tolerability
- Phase 2
  - Effectiveness
- Phase 3
  - Safety
- Phase 4
  - Post Marketing
**Drug Treatment**

**Biomarkers and Outcome**

- **Drug Treatment**
  - Disease Modifying
  - Symptomatic

- **Disease** (weeks or months)
- **Pathology** (months, years, decades)
- **Illness**

**Biomarker**
- e.g. tumour size

**Outcome**
- e.g. death

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**Terminology: definitions**

- **Biomarker**
  - Readily measurable marker of response
  - e.g. Drop in blood pressure, lowering of plasma glucose concentration

- **Surrogate endpoint**
  - Biomarker used for Regulatory Approval
  - e.g. Reduction in viral load, CD4+ cell count, plasma cholesterol concentration

- **Outcome**
  - What the patient feels/functions/survives
  - e.g. pain/hospital admission/surgery/death

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**Biomarker**

**EEG Slowing**

![Graph showing EEG Slowing](image_url)
Surrogate Endpoint

HIV viral load and CD4 count

Enfuvirtide, an HIV-1 Fusion Inhibitor, for Drug-Resistant HIV Infection in North and South America

At 24 weeks, the change from baseline in the viral load (intention-to-treat, last observation carried forward) was a decrease of 1.696 in the enfuvirtide group, and a decrease of 0.764 log 10 copies per milliliter in the control group (P<0.001).

The mean increases in CD4+ cell count were 76 cells per cubic millimeter and 32 cells per cubic millimeter, respectively (P<0.001).”

Lalezari et al. NEJM 2003

Clinical Outcome

Decreased Risk of Death

Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)


Biomarkers vs. surrogate endpoints

- Biomarkers reflect an important feature of a disease, so reliably reflect biological response to drug
  - this is not the same as therapeutic response in terms of improved patients outcomes

- Surrogate endpoints are supposed to be readily measurable biomarkers that closely reflect eventual clinical outcomes
  - a laboratory substitute for a clinically meaningful result, causally linking disease with outcome
Examples of biomarkers, surrogate endpoints and clinical outcomes

<table>
<thead>
<tr>
<th>Therapeutic class</th>
<th>Biomarker/surrogate</th>
<th>Clinical endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive drugs</td>
<td>↓Blood pressure</td>
<td>↓Stroke</td>
</tr>
<tr>
<td>Drugs for glucosuria</td>
<td>↓ Intracocular pressure</td>
<td>Preservation of vision</td>
</tr>
<tr>
<td>Drugs for osteoporosis</td>
<td>↑Bone density</td>
<td>↑Fracture rate</td>
</tr>
<tr>
<td>Antihistamine drugs</td>
<td>↓Anxiety</td>
<td>↑Survival</td>
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<tr>
<td>Laboratory workers</td>
<td>&quot;Negative culture&quot;</td>
<td>&quot;Clinical cure&quot;</td>
</tr>
<tr>
<td>Anticonvulsant drugs</td>
<td>↑CD4 count, ↓ viral RNA</td>
<td>↑Survival</td>
</tr>
<tr>
<td>Antidiabetic drugs</td>
<td>↓Blood glucose</td>
<td>↑Morbidity</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td>↓Cholesterol</td>
<td>↓Coronary artery disease</td>
</tr>
<tr>
<td>Drugs for prostate cancer</td>
<td>↓Prostate-specific antigen</td>
<td>↑Tumor response</td>
</tr>
</tbody>
</table>

Important characteristics & distinctions

- **Biomarkers**
  - Repeated measurements possible
  - Usually cheap
  - Often high content information
  - Often give rapid indication of response
  - Can be of prognostic or diagnostic value

- **Clinical Outcome**
  - Subjective (e.g. pain)
  - Often only happens once (e.g. death)
  - Can take many years for differences to be evident

Information Content

- **Biomarker e.g. Blood Pressure**
  - 40-300 mmHg
  - 2-3 decimal digits
  - High information

- **Clinical Outcome e.g. Death**
  - Dead or alive
  - Only 1 binary digit
  - Low information
The Problem of Biomarkers
The Responder Paradox

- Blood Pressure lowering is predictable
  » Blood pressure is lowered in nearly all patients who are treated

- Blood pressure rarely predicts individual beneficial Clinical Outcome
  » Only a small percentage of patients will have death or disability prevented
  » A larger percentage will have adverse effects

Biomarkers and outcomes
Independent, linked, causative....?

Two trials show the beneficial effects of lowering blood pressure and reducing stroke


Biomarkers – blood pressure
Secondary prevention trial for stroke

Eprosartan is an angiotensin-II receptor antagonist. Nitrendipine is a calcium channel blocker

Outcomes – clinical events

The combined primary endpoints of mortality plus the total number of cardiovascular events and cerebrovascular events was reduced by eprosartan compared to nitrendipine. The difference emerges after 1 year and becomes more pronounced with follow-up.

Blood Pressure is Not a Good Surrogate Endpoint

- Biomarker (BP) data would predict equal effectiveness of treatments
- Outcome assessment reveals marked differences between treatments!
- Disease processes are complex and outcomes are subject to many variables that are not always reflected adequately by measuring a simple biomarker

Surrogates are Cost Effective

- Surrogate Endpoint
  » High information
  » Low Cost
  » "Accepted" to be strongly correlated with outcome
- Using Surrogate Endpoint instead of Outcome
  » cheaper and shorter clinical trials
New formulations and generics

- Drug concentration is the most widely used surrogate endpoint
- Formulations with equivalent rate and extent of absorption are considered interchangeable
- No clinical outcome required
- Generic drugs are a BIG industry

Is the Drug Safe?
(toxicity and adverse events)

- Adverse Events are hard to detect
- Some are predictable from pharmacological mechanism
  » e.g. BP lowering leads to fainting
- Many are idiosyncratic ('individual mix') and difficult to predict in the individual
  » e.g. dry cough associated with ACE inhibitors

Phases of Drug Development
Safety and monitoring

- Phase 0
  » Predictions for Humans
- Phase 1
  » Tolerability
- Phase 2
  » Effectiveness
- Phase 3
  » Safety
- Phase 4
  » Post Marketing
  Adverse event assessment & monitoring
Adverse Event Detection

- Clinical outcomes can be hard to observe and connect to drug exposure
  - Phase 3 – Systematic from trained monitor
  - Phase 4 – Spontaneous reports from clinicians
  - Causality, timing, plausibility, dose-response?

NZ Pharmacovigilance Centre
In Dunedin at University of Otago
https://nzphvc.otago.ac.nz/carm-adr/
Centre for Adverse Reactions Monitoring (CARM)
Intensive Medicines Monitoring Programme (IMMP)
iPhone App available for making reports

Adverse Event Detection
Toxicity monitoring

- Biomarker/Surrogate Endpoints
  - Liver: ALT (alanine aminotransferase)
  - Kidney: Serum creatinine
  - Heart: QT Interval

Conclusions

- Biomarkers are essential for learning and understanding clinical pharmacology
- Surrogate Endpoints are optional (but commercially important) for regulatory decisions
- Clinical Outcome is essential before new drugs are licensed for patients