PHA 3021
Drugs in Health and Disease

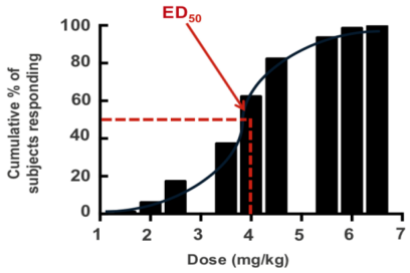
Introduction to Principles of Therapeutics

Rationale

1. Requires knowledge of expected results <u>before</u> commencing therapy
   - Efficacy, Lower limits of toxicity
2. Use endpoints to monitor progress and signal the need for change – right drug and right dose
   - Different Dose (quantitative)
   - Different Drug (qualitative)
3. Correct Diagnosis by understanding disease pathophysiology
4. Understanding pharmacology of potentially useful drugs – kinetics, efficacy, metabolism, adverse
5. Optimising selection of drug/ choice of therapy

Therapeutic Context

Efficacy, effectiveness, ceiling effect: The maximal effect obtained by a drug
Potency: The dose required to have a specific effect – more potent, smaller dose
Dose/Response: Graded on a continuous logarithmic scale
Graded ED_{50} – Dose required to obtain 50% of the maximum effect



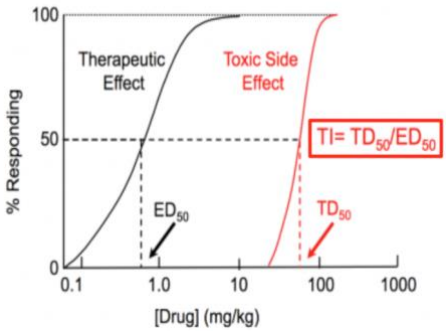
Quantal Dose/Response Relationships

- Bell shaped curve for the population
- Related to frequency of all or nothing effect
- **QED_{50}** : Dose at which 50% of subjects exhibit the specified effect

Therapeutic vs. Toxic Effects: Therapeutic Index

$TI = TD_{50} / ED_{50}$

- Represents the measure of the margin of safety
- TD_{50}: Dose producing toxic endpoint in 50% of population
- ED_{50}: Dose producing therapeutic endpoint in 50% of population
- Used to use Lethal Dose LD_{50} – Dose which kills 50% of population, yet everyone will have therapeutic effect before it kills
- Minor headache: low effective dose and no toxicity
- Cancer: Will tolerate some toxicity e.g. chemotherapy



Applies Pharmacokinetics

1. Parameters needed for calculation dose
   - Volume of Distribution – V_d
   - Clearance – Cl
   - Half Life – $t_{1/2}$
2. Target concentration: need efficacy but avoid toxicity
3. Loading dose: Calculated to rapidly induce effective plasma [drug]
4. Maintenance dose: via infusion, repeated dosing if short half life
5. Age, pregnancy, health status, pharmacogenetics (fast and slow metabolisers)

Digoxin

- Cardiac glycoside used to heart failure
- Long half-life and large Vd with a low therapeutic index
- Increased toxicity in setting of hypokalaemia (low plasma K+)

TGN1412

- Monoclonal antibody targeting T-cell receptor
- Super agonist to promote T-cell activation
- Caused a cytokine storm, causing multiple organ failure and hospitalisation
- Now follow a single dose trial

BIA 10-2472

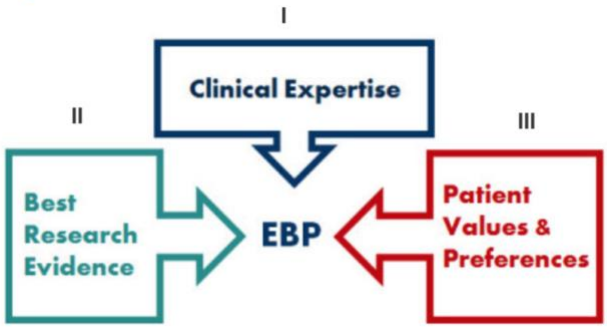
- Fatty acid amide hydrolase inhibitor to increase endogenous cannabinoids
- First trial no effects, but the second dose had all hospitalised and one dead
- Was an adaptive study, that changed the trial and did not need to report it
- Interval dosing between each subject is now required

Vioxx

- COX 1 generated prostaglandin for protection of stomach lining and platelet aggregation
- COX 2 is the inducible isoform, generates prostaglandin involved in inflammation
- VIGOR study found is was selective for COX 2 only and equally effective
- Found to have an increased incidence of stroke and heart attack
- Removed off the market after 4 years

Evidence Based Medicine

The integration of **individual clinical expertise** with the **best available external clinical evidence** from systematic research and patients **values and expectation**



Individual Clinical Expertise

- Clinical skills and clinical judgement
- Depends if it is useful for patient. i.e. not females due to reproductive issues

Best External Evidence

- From real clinical research
- Rapidly changing landscape
- Replaces currently accepted treatments and diagnostic tests with new ones

Patients Values and Expectations

Have always played a central role in determining

- Whether interventions take place
- Which interventions take place

i.e. Resistance by a patient

EBM Is Not

Not Cook Book Medicine

- Evidence needs extrapolation to patient's unique biology and values

Not Cost Cutting Medicine

- When efficacy for the patient is paramount, costs may rise

The 5 A's

Assess and Ask – Start with the patient – clinical problem and construct a well-built clinical question it
Acquire – Select the appropriate resources
Appraise – The evidence for its validity and applicability
Apply – Return and talk with patient and ingrate the evidence
Self-Evaluation – Evaluate your performance with this patient

Levels of Evidence

Level 4 – Case Series (Weakest)

- Descriptive study that is not analytical
- No control group
- Do not test a hypothesis between treatment outcome
- May generate a hypothesis for a clinical trial

Level 2+3 – Clinical Trials

Compare treatments and interventions
Randomised – limit bias
Controlled – To compare with no treatment
Blinded/Double Blinded – to minimise potential placebo effect
Crossover – Design where patient acts as own control

Level 1 – Systematic Reviews (Strongest)

Combining Controlled Clinical Trials using:
Cochrane Collaboration

- Combines drugs and diseases together
- Is a search engine

Problems with Evidence from Trials

- Narrow question posed and funded by big pharma
- Easily measurable surrogate parameters

Absolute vs. Relative Risk Reduction

Absolute
Event Rate 5% - 3.5% = 1.5%
Relative Risk Reduction
= 1 – (treatment/placebo) X 100

	Subjects	Deaths	Event rate
Placebo	2000	100	5%
Treatment	2000	70	3.5%

In comparison:
= 50% **better** at lowering BP than drug A

- However, it does not lower BP by 50%
- Probably under-powered to show mortality benefit

	Subjects	SBP at 1 yr	ΔSBP
state-of-the-art (Drug A + B)	500	160	-40
me-too add-on (Drug A + C)	500	140	-60

Appraise

- How true and valid are the results
- Cochrane reviews influences policy and practice
- Provides “Clinical Guidelines”
- Doctors likely to use EBM has better results for patients

E.g. Antibiotics use should not routinely be used for sore throat or middle ear infections

Torcetrapib

- Claimed to reduced CV events in patients by reducing LDL by increasing HDL
- Found that increased blood pressure and CV events even with a high HDL
- Poor evidence based meets big pharma due to potential $10 billion market

Apply

- Adherence due to some reported risks. i.e. statins increase diabetes possibility but assist in decreasing CV risk so should still be taken