Predicting and Preventing Adverse Drug Reactions and Interactions

Malcolm Tingle

"Those who don't know history are destined to repeat it"

Edmund Burke (1729-1797)

Definitions

1. Adverse Event (or Adverse Experience)
   Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

2. Adverse Drug Reaction (ADR)
   In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.
   • Unexpected Adverse Drug Reaction
     An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator’s Brochure for an unapproved investigational medicinal product).
Liverpool Causality Tool for ADR

Severe vs. Serious

- The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache).
- This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning.

Serious ADR

- A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:
  - results in death
  - is life-threatening
  - requires inpatient hospitalisation or results in prolongation of existing hospitalisation
  - * results in persistent or significant disability/incapacity
  - is a congenital anomaly/birth defect
  - * is a medically important event or reaction.
Common Terminology Criteria for Adverse Events: Severity Grades

1. Mild: symptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2. Moderate: minimal, local or non-invasive intervention indicated; - limiting age-dependent daily living such as preparing meals, shopping, telephone, managing money
3. Severe or medically-significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation; disabling -limiting bathing, (un)dressing, use of toilet, taking medications
4. Life-threatening consequences: urgent intervention indicated
5. Death

ADR –Dependent Hospital Admissions in the UK

• **Design** Prospective observational study.
• **Setting** Two large general hospitals in Merseyside, England.
• **Participants** 18,820 patients aged > 16 years admitted over six months and assessed for cause of admission.
• **Main outcome measures** Prevalence of admissions due to an ADR, length of stay, avoidability and outcome.


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Results

There were 1225 admissions related to an ADR, giving a prevalence of 6.5%:
- ADR directly leading to the admission in 80% of cases.
- The median bed stay was eight days, accounting for 4% of the hospital bed capacity.
- The projected annual cost of such admissions to the NHS is £466m (£670m, €847m).
- The overall fatality was 0.15%.
- Most reactions were either definitely or possibly avoidable.
- Drugs most commonly implicated in causing these admissions included low dose aspirin, diuretics, warfarin, and non-steroidal anti-inflammatory drugs other than aspirin, the most common reaction being gastrointestinal bleeding.

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Drug-Related Deaths in Europe

• A systematic review of drug-related deaths in patients requiring hospitalisation or whilst hospitalised suggest an overall rate of 7.3%
• During hospitalisation, acquired DRD represented 2.7% of deaths and occurred in 0.05% of hospitalised patients.
  - Doesn’t sound much but = 1 in 2000

Medication-related patient harm in NZ hospitals: 2013-2015

Table 5: NIM categories.

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category A:</td>
<td>No harm</td>
</tr>
<tr>
<td>Category B:</td>
<td>Temporary harm to the patient and required intervention</td>
</tr>
<tr>
<td>Category C:</td>
<td>Temporary harm to the patient and required initial or prolonged hospitalisation</td>
</tr>
<tr>
<td>Category D:</td>
<td>Permanent patient harm</td>
</tr>
<tr>
<td>Category E:</td>
<td>Interventions required to sustain life</td>
</tr>
<tr>
<td>Category F:</td>
<td>Patient death</td>
</tr>
</tbody>
</table>
Medication-related patient harm in NZ hospitals: 2013-2015

Table 6: Medication-related patient harm in NZ hospitals: 2013-2015

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident</td>
<td>Medication-related harm occurred during hospital admission</td>
<td>Patient had anaphylactic reaction to chlorohydrin.</td>
</tr>
<tr>
<td>Suspected</td>
<td>Medication-related harm occurred related to a prior discharge within 30 days of the index admission</td>
<td>Patient admitted with sepsis and discharged after being discharged on antibiotics.</td>
</tr>
<tr>
<td>Incident</td>
<td>Medication-related harm that occurred in the community and referred to an admission.</td>
<td>Patient on metoprolol admitted with a Severe due to still bleeding from a liposarcoma.</td>
</tr>
</tbody>
</table>

Table 7: Medication-related patient harm by harm severity and risk.

<table>
<thead>
<tr>
<th>Risk Type</th>
<th>Important</th>
<th>Non-Important</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>400</td>
<td>47</td>
<td>447</td>
</tr>
<tr>
<td>F</td>
<td>90</td>
<td>148</td>
<td>238</td>
</tr>
<tr>
<td>G</td>
<td>83</td>
<td>167</td>
<td>250</td>
</tr>
<tr>
<td>G</td>
<td>26</td>
<td>51</td>
<td>77</td>
</tr>
<tr>
<td>G</td>
<td>5</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>I</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>669</td>
<td>399</td>
<td>1068</td>
</tr>
</tbody>
</table>

Table 8: Medication implicated in patient harm by harm severity.

<table>
<thead>
<tr>
<th>Medication class</th>
<th>Important</th>
<th>Non-Important</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsteroidal anti-inflammatory agents</td>
<td>29</td>
<td>52</td>
<td>81</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>30</td>
<td>26</td>
<td>56</td>
</tr>
<tr>
<td>Beta-blockers, angiotensin-converting-enzyme inhibitors, and other antihypertensives</td>
<td>13</td>
<td>27</td>
<td>40</td>
</tr>
<tr>
<td>Diuretics</td>
<td>24</td>
<td>23</td>
<td>47</td>
</tr>
<tr>
<td>Other cardiovascular medications (ACE inhibitors, ARBs, calcium channel blockers)</td>
<td>14</td>
<td>15</td>
<td>29</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>56</td>
<td>1</td>
<td>57</td>
</tr>
<tr>
<td>Other groups of medications with less than 30 harms recorded</td>
<td>122</td>
<td>88</td>
<td>210</td>
</tr>
<tr>
<td>Total</td>
<td>562</td>
<td>324</td>
<td>886</td>
</tr>
</tbody>
</table>

Figure 5: Adverse reactions to medicines, vaccines and CARH reported to the ANZ Centre for Adverse Reactions Monitoring, 2017-2018

ADR Mechanisms

The mechanisms involved may vary widely, but involves:

- Interaction with receptor or enzymes (pharmacological?)
  - Type I or A: Predictable, dose-dependent based on the known pharmacology of the drug
  - Type II or B: Not predictable, no clear dose-dependency and not due to the known pharmacology of the drug

- Alteration of structural proteins, DNA or Lipids (chemical)

Safe versus Toxic Dose

- Reactions are due to the known pharmacology of the drug and are therefore dose-dependent and predictable

  - Take too much drug (wrong dose/frequency/duration)
  - Take 2 or more drugs with overlapping pharmacology
  - Take 2 drugs or more that have metabolic interaction

Medication-related patient harm in NZ hospitals: 2013-2015

<table>
<thead>
<tr>
<th>Medication classes</th>
<th>E</th>
<th>P</th>
<th>E</th>
<th>I</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids (including transdermal)</td>
<td>250</td>
<td>15</td>
<td>0</td>
<td>265</td>
<td>10.44%</td>
<td></td>
</tr>
<tr>
<td>Anti-infective/antimicrobial agents</td>
<td>25</td>
<td>52</td>
<td>0</td>
<td>77</td>
<td>3.13%</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>40</td>
<td>26</td>
<td>1</td>
<td>71</td>
<td>7.26%</td>
<td></td>
</tr>
<tr>
<td>Beta blockers, calcium channel blockers and other antihypertensive agents</td>
<td>56</td>
<td>27</td>
<td>1</td>
<td>84</td>
<td>10.02%</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>14</td>
<td>25</td>
<td>1</td>
<td>39</td>
<td>4.05%</td>
<td></td>
</tr>
<tr>
<td>Other cardiovascular medications (ACE inhibitors, ARBs, central acting agents, aldosterone agents)</td>
<td>10</td>
<td>15</td>
<td>1</td>
<td>36</td>
<td>3.85%</td>
<td></td>
</tr>
<tr>
<td>Not recorded, same protocol</td>
<td>70</td>
<td>56</td>
<td>4</td>
<td>130</td>
<td>14.24%</td>
<td></td>
</tr>
<tr>
<td>Other groups of medicines with less than 50 harms recorded</td>
<td>122</td>
<td>88</td>
<td>0</td>
<td>211</td>
<td>22.8%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>745</td>
<td>523</td>
<td>19</td>
<td>1014</td>
<td>100.00%</td>
<td></td>
</tr>
</tbody>
</table>

Drug death: Nurse stood down

By Andrea Main
5:35 AM Friday May 13, 2011

A North Shore hospital nurse with an "unknown drug reaction" has been stood down after a 60-year-old grandmother died when she was given 15 times too much heart medication.

Shirley Cui, who had earlier had a triple bypass operation, was admitted to North Shore Hospital with breathing problems and went into cardia arrest just before 8am.

She was treated for five days and was due to be discharged.

But she received 15 times the prescribed dose of metoprolol, a beta-blocker which slows the heart.

"Things were going off and red lights were flashing and they said they can't get a pulse and I just burst into tears," nurse Donna Stimson told One News.

"We were told that the doctor had prescribed 1.25mg and the nurse had given her 17.5mg, which caused severe heart failure and then multi-organ failure."

Medication-related patient harm in NZ hospitals: 2013-2015

Table 2: Medications implicated in patient harms by harm severity

<table>
<thead>
<tr>
<th>Medication class</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids (includes tramadol)</td>
<td>20</td>
<td>10</td>
<td>0</td>
<td>26</td>
<td>5</td>
<td>105</td>
</tr>
<tr>
<td>Anti-infective/antimicrobial agents</td>
<td>29</td>
<td>32</td>
<td>6</td>
<td>3</td>
<td>108</td>
<td>8.1%</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>40</td>
<td>16</td>
<td>1</td>
<td>11</td>
<td>71</td>
<td>5.4%</td>
</tr>
<tr>
<td>Beta-blockers, calcium channel blockers and other antihypertensive agents</td>
<td>20</td>
<td>27</td>
<td>1</td>
<td>6</td>
<td>54</td>
<td>4.2%</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>20</td>
<td>23</td>
<td>1</td>
<td>2</td>
<td>50</td>
<td>3.5%</td>
</tr>
<tr>
<td>Other combinations of medications (ACE inhibitors, ARBs, anticoagulants, anti-hypertensives)</td>
<td>18</td>
<td>15</td>
<td>1</td>
<td>16</td>
<td>56</td>
<td>4.2%</td>
</tr>
<tr>
<td>Other groups of medications with less than 30 harms recorded</td>
<td>50</td>
<td>35</td>
<td>4</td>
<td>4</td>
<td>133</td>
<td>10.1%</td>
</tr>
<tr>
<td>Total</td>
<td>560</td>
<td>124</td>
<td>12</td>
<td>3</td>
<td>303</td>
<td>233.9%</td>
</tr>
</tbody>
</table>


Efficacy and toxicity of antihypertensive pharmacotherapy relative to effective dose 50

British Journal of Clinical Pharmacology, First published: 20 June 2019, DOI: (10.1111/bcp.14033)
Preventability of Adverse Drug Reactions: Schumock & Thornton

• Was the drug involved in the ADR not considered appropriate for the patient’s clinical condition?
• Was the dose, route, and frequency of administration not appropriate for the patient’s age, weight and disease state?
• Was the require therapeutic drug monitoring or other laboratory test not performed?
• Was there a history of allergy or previous reactions to the drug?
• Was a drug interaction involved in the reaction?
• Was a toxic serum drug level documented?
• Was poor compliance involved in the reaction?


Preventing ADR

‘Safety Pharmacology’

Jean-Pierre Valentin, Russell Bialecki, Lorna Ewart, Tim Hammond, Derek Leishmann, Silvana Lindgren, Vicente...


http://dx.doi.org/10.1016/j.vascn.2009.05.011
Limitations of Animal Testing

- There are many limitations to evaluation of drug toxicity in animals including:
  - Limited choice of species for various tests
  - Species switching between tests
  - Interspecies variability in metabolism
  - Interspecies variability in response
  - Lack of subjective ADR
  - Lack of suitable models for many human ADRs (e.g. hypersensitivity reactions)

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Efficacy Guidelines

- CLINICAL SAFETY
  - E1 The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions
  - E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
  - E2B(R2) Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports
  - E2C(R1) Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs
  - E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting
  - E2F Development Safety Update Report

- CLINICAL STUDY REPORTS
  - E3 Structure and Content of Clinical Study Reports

- DOSE-RESPONSE STUDIES
  - E4 Dose-Response Information to Support Drug Registration

- ETHNIC FACTORS
  - E5(R1) Ethnic Factors in the Acceptability of Foreign Clinical Data

- GOOD CLINICAL PRACTICE
  - E6(R1) Good Clinical Practice: Consolidated Guideline

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Efficacy Guidelines

- CLINICAL TRIALS
  - E7 Clinical Evaluation of Special Populations: Geriatrics
  - E8 General Considerations for Clinical Trials
  - E9 Statistical Principles for Clinical Trials
  - E10 Choice of Control Group and Related Issues in Clinical Trials
  - E11 Clinical Investigation of Medicinal Products in the Pediatric Population

- PRINCIPLES FOR CLINICAL EVALUATION BY THERAPEUTIC CATEGORY
  - E13 Principles for Clinical Evaluation of New Antihypertensive Drugs

- PHARMACOGENOMICS
  - E14 The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs
  - E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories
  - E16 Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions
Clinical Volunteers and TGN 1412
March 13 2006.

• 8 Men took part in a phase I trial for a monoclonal antibody TGN 1412
  – immunomodulatory humanized agonistic anti-CD28 monoclonal antibody
  – developed for the treatment of immunological diseases, e.g. multiple sclerosis, rheumatoid arthritis and certain cancers

### Name | Eligibility
--- | ---
Spartan study | Healthy males and females of non child bearing potential
  | Aged 25-55 years; BMI 18-30kg/m²; Non-smoker; No medications

Oracle study | ASIAN males (specifically Chinese, Japanese, Korean, Vietnamese or Taiwanese)
  | Aged 18 – 55 years; BMI 18 to 30kg/m²; Non-smoker; No medications

Neon MAD study | Healthy males and females
  | Aged 18-55years; BMI 19-35kg/m²; Non-smoker; No medications.

Zephyr study | Healthy males and females
  | Aged 18-60 years; BMI 18-32kg/m²; Non-smoker; No medications; No history of asthma (including childhood asthma)

Popeye study | Healthy males and females of non child bearing potential
  | Aged 18-55 years; BMI 18-30kg/m²; Non-smoker; No medications.

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### Doses, Administration and times

All subjects were dosed between 6-9 AM on the 15th Mar 2006 at -1 Hazinee intervals.
They received active agent and two matched placebos.

<table>
<thead>
<tr>
<th>Subject</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (Kg)</td>
<td>4.0</td>
<td>4.0</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>500</td>
<td>500</td>
<td>475</td>
<td>475</td>
<td>475</td>
<td>475</td>
</tr>
<tr>
<td>Dose (mg/kg)</td>
<td>500</td>
<td>500</td>
<td>475</td>
<td>475</td>
<td>475</td>
<td>475</td>
</tr>
<tr>
<td>Dose/time</td>
<td>00:00</td>
<td>00:20</td>
<td>00:50</td>
<td>08:00</td>
<td>08:50</td>
<td>09:50</td>
</tr>
</tbody>
</table>

### Symptoms and timing

A number of reactions were reported by the subjects daily after administration of the investigational agent (placebo).

- In 5 of 6 subjects, headache was reported between 56-60 minutes.
- All reported muscular aches.
- Rigors were reported between 38.4-38.8 minutes in 4 subjects.
- Elevated temperatures >39°C were noted between 2.9 to 6.5 hrs.
- Hypotension was noted between 5.5 to 4.6 hrs after administration.
- Tachycardia noted at 2.5 to 4.6 hrs.

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Accessed: 22 June 2018

The report made 22 recommendations

- “Special consideration should be given to new agents for which the primary pharmacological action, for the proposed therapeutic effect, cannot be demonstrated in an animal model”

- “When it is likely that pre-clinical information, for any reason, may be a poor guide to human responses in vivo, the starting doses in first-in-man trials should be calculated to err on the side of caution”

- “New agents in first-in-man trials should be administered sequentially to subjects with an appropriate period of observation between dosing of individual subjects”
Why Humans?

- TGN 1412 interacts with 15 amino acids on the receptor.
- Differences of up to 4% (9 of 220 amino acids) between rhesus and human CD28 have been found.
  - Two variable positions in the rhesus CD28 sequence — amino acid 65 (glutamic acid or glycine) and 104 (asparagine or tyrosine) — are located on the edge of the contact region between human CD28 and TGN1412.
  - They are likely to substantially affect the strength of antibody–antigen interaction.
  - Monkeys only had swollen lymph nodes.

References:

Or...

- Mast cells also have CD28.
- Activation of mast cells causes release of histamine and 5-HT.
  - Mediators in anaphylaxis causing rapid increased vascular permeability, bronchoconstriction and nausea.
- Also get release of TNFs and cytokines (e.g. IL-2, IL-4).
  - Responsible for “late-phase” reactions including vascular permeability and leukocyte infiltration.
- There are species-, inter-individual-, and tissue-differences in responsiveness of mast cells that limit extrapolation of animal & in vitro data to the clinic.

References:
Systemic release of IL-10, but not pro-inflammatory cytokines, by TAB08 in healthy volunteers

In the ill-fated FHI trial of TGN1412 in 2006, healthy volunteers (n=5) received a bolus injection of 100 μg/kg body weight, which led to a systemic release of pro-inflammatory cytokines, most notably TNF, IFN-γ, and IL-2, but also of IL-10, suggesting that both CD4+ EM and Treg cells had been activated [19]. In a new study, much lower doses of TAB08 were therefore applied under close clinical surveillance, starting with 0.1 μg/kg (1000-fold less than applied in the London trial), followed by several intermediate doses and a maximal dose of 7 μg/kg. The
The need for Pharmacovigilance

- Clinical trials may fail to identify rare adverse reactions
  - Many ADR mimic spontaneously occurring medical conditions, so incidence is not 0 in the control population
  - A low incidence may occur in the clinical trials due to patient selection criteria or duration of trials
- ADR do not occur in the context of the trials
  - Dosage may be increased post-marketing to “increase effectiveness”
  - May be used for long-term indications
  - Interactions may occur with new drugs not previously screened
  - Used for new indications
Inter-individual Variability & 'Type II' ADR

Can We Predict the 'Unpredictable' and Prevent ADR?
Inter-individual Variability in Drug Metabolism

- Lack of metabolism: enhanced plasma concentrations and exaggerated pharmacological responses.
- Lack of a metabolic pathway in certain individuals: compound is bioactivated by a different enzyme.
- Enhanced toxicity due the lack of a detoxification pathway.
- Lack of a bioactivation pathway: poor metabolisers at less risk.
- Increased protein expression or catalytic activity, with subsequent increase in the formation of toxic metabolites.

Lack of detoxication resulting in secondary effects: Perhexiline

- Perhexiline is an anti-angina drug that has cationic, amphiphilic properties.
- If it is not metabolised (by CYP2D6), perhexiline accumulates in lysosomes resulting in hepatotoxicity and neuropathy.

Perhexiline

- In UK, a total of 543 reports of ADR, with 20 fatal
- Withdrawn from most of the world but…. 
- In NZ:

Monitoring of Plasma Levels

Plasma perhexiline concentrations should be maintained between 0.15 and 0.60 mcg/ml. Because of perhexiline's slow and variable clearance, the marked inter-subject variability in metabolism of the medicine and the potential for serious toxicity, regular monitoring of plasma levels of perhexiline is essential commencing at the end of the first week of use. Dosage should not be increased unless the plasma concentrations are sub-therapeutic and at least two to four weeks have elapsed since commencement, or last increase in dose, of perhexiline. If facilities for determining plasma levels are not available, PEXSIG should not be prescribed.

Patients may respond differently to codeine and some patients may be at increased risk of serious adverse effects. Symptoms of codeine toxicity or overdose may include somnolence, difficulty waking, confusion, shallow breathing, nausea and vomiting.

Treatment of codeine toxicity is most commonly with the opioid antagonist, naloxone. Prescribers are reminded that patients may respond differently to codeine treatment and are encouraged to educate parents and caregivers of young patients about possible adverse effects associated with codeine use.

Codeine is a widely used opioid analgesic and is sometimes given post-operatively for pain relief in children. Codeine has a very low affinity for opioid receptors and is partially metabolised to morphine in the liver via the cytochrome P450 enzyme 2D6 (CYP2D6).

Genetic differences in the expression of the CYP2D6 enzyme results in differences in the extent to which codeine is metabolised. Patients deficient in or lacking this enzyme cannot convert codeine to morphine and therefore may not obtain adequate analgesic pain relief. Conversely, patients who metabolise codeine very rapidly (ultra-rapid metabolisers) are at increased risk of developing adverse effects of opioid toxicity, even at low doses.

Estimates suggest that up to 10% of the Caucasian population may be poor metabolisers and up to 10% may be ultra-rapid metabolisers. The prevalence in Maori and Pacific people is not known. Genetic testing to identify ultra-rapid metabolisers prior to prescribing codeine is not currently available in New Zealand.

Recently, cases of respiratory depression and death following the use of codeine for post-surgery analgesia have been reported in the medical literature. These incidents occurred in children who had evidence of being ultra-rapid metabolisers of codeine. Post-operative codeine use after surgeries such as tonsillectomy or adenoidectomy may increase the risk of breathing difficulties in susceptible children. Symptoms of codeine toxicity or overdose may include nausea, vomiting, constipation, lack of appetite, somnolence, adverse interactions, respiratory depression and death. Caregivers and patients should be advised to immediately discontinue codeine and seek medical attention if these symptoms occur.

Effects can be reversed with naloxone, a narcotic antagonist. Naloxone acts by competing for the same receptor sites as opioids.

References
HLA-B*5701 genotype in DILI due to flucloxacillin

• ~1 in 500 - 1,000 individuals with this genotype will develop DILI when treated with flucloxacillin.
  – No use as a ‘predictor’
  – Clinically, HLA-B*5701 genotyping of suspected cases of flucloxacillin DILI may prove to be a useful diagnostic test
  – If a prompt test is available, substituting flucloxacillin with alternative anti-staphylococcal agents such as cloxacillin and dicloxacillin in these suspected cases should be feasible


Azathioprine & 6-Mercaptopurine

• Azathioprine is used as an immunosuppressant in Crohn’s disease and organ transplantation
• Its metabolite, 6-MP, is used for acute lymphoblastic leukaemia & acute myelogenous leukaemia
• 6-MP works by
  – blockade of protein -SH groups by alkylation.
  – inhibition of nucleic acid biosynthesis, hence proliferation and immune responses
  – Direct damage to DNA by incorporation of purine thio analogues

Treatment with 6-MP may cause bone marrow suppression, leading to leucopenia, thrombocytopenia and, less frequently, anaemia
  – Pharmacokinetic interaction with xanthine oxidase inhibitors (e.g. allopurinol)
  – Patients deficient in Thiopurine Methyl Transferase (TPMT)
TPMT

89% of individuals have high TPMT activity, 11% have intermediate activity and ~1 in 300 patients are at high risk of potentially fatal haematopoietic toxicity

- TPMT activity exhibits autosomal co-dominant genetic polymorphism: there are 2 main mutant alleles in humans, TPMT*2 and TPMT*3A (~75% of mutations)
- The mechanism(s) for loss of activity have not been fully elucidated, although the mutant proteins have a shorter t½ than the wild type (TPMT*1)
- Toxicity is due to accumulation of thioguanine nucleotides in haematopoietic tissues
- Dose reduction in patients is necessary

More then TPMT....

- TPMT genotype does not predict adverse drug reactions to thiopurine drugs in patients with inflammatory bowel disease
- Mutations in IMPDH1 & GMPs appear exclusively in patients with severe thiopurine resistance
- Leads to less of the active metabolite (STGN) and more of 6MMP which may be hepatotoxic

References:
PHENOTYPE versus GENOTYPE

- Possible to determine TPMT enzyme activity
  - now routine in New Zealand: used to predict severe leucopenia in 1:200 cases of deficiency

- 6-TGN & 6-MMP determination in RBC
  - becoming routine in New Zealand
  - 6-TGN range 235 – 450 pmol/8x10^8 RBC
  - 6-MMP <5700 pmol/8x10^8 RBC

- Very poor correlation between AZA dose and 6-TGN concentration (r^2 = 0.002):
  - Need to monitor 6-TGN concentrations instead of relying on dose per kg body weight to individualize therapy.

Warfarin

- Warfarin is used in the prophylaxis and treatment of venous thrombosis & pulmonary embolism
  - It inhibits the synthesis of vitamin K dependent coagulation factors
  - This results in a sequential depression of Factors II, VII, IX and X activities

- In overdose or poisoning:
  - Appearance of blood in stools or urine, haematuria, excessive menstrual bleeding, excessive bruising or persistent oozing from superficial injuries (early signs)
  - Necrosis and/or gangrene of skin and other tissues, which may require amputation
  - Death: It is also used as a rodenticide!
Warfarin Mode of Action

- Warfarin inhibits the vitamin K epoxide reductase multi-protein complex (VKOR)
- The Vitamin K Epoxide Reductase Complex, Subunit 1 gene (VKORC1) encodes a small transmembrane protein of the endoplasmic reticulum
  - Missense mutations of VKORC1 lead to warfarin resistance
  - Patients with the mutation require a higher dose

Warfarin Metabolism

• Warfarin is racemic:
  – the S-isomer is 3-5 times more potent than the R-isomer.
• S -Warfarin is metabolised by CYP2C9 to the 7-hydroxy metabolite.
  – R-warfarin inhibits this metabolic clearance.

• Allelic variants CYP2C9*2 and CYP2C9*3 differ from CYP2C9*1 by single amino acid substitutions:
  – The allelic variants are associated with impaired hydroxylation of S-warfarin.
  – There is a strong association between CYP2C9 variant alleles and low warfarin dose requirements.
  – “CYP2C9 genotyping may identify a subgroup of patients who have difficulty at induction of warfarin therapy and are potentially at a higher risk of bleeding complications.”

Aithal GP, Day CP, Kesteven PJL, Daly AK. Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. The Lancet 1999; 353: 717-9

Warfarin Pharmacogenomics

• In a study, combining the CYP2C9*2, CYP2C9*3, and VKORC1 1173C>T genotype results, as much as 56% of the inter-individual variability of the warfarin pharmacodynamic response.
• Large inter-ethnic variability in allele frequencies.

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>CYP2C9*2</th>
<th>CYP2C9*3</th>
<th>VKORC1 1173C&gt;T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>0.9-20%</td>
<td>0-14.5%</td>
<td>37%</td>
</tr>
<tr>
<td>African</td>
<td>0.8-7%</td>
<td>0.4-3%</td>
<td>14%</td>
</tr>
<tr>
<td>Asian</td>
<td>0%</td>
<td>0-8.2%</td>
<td>89%</td>
</tr>
</tbody>
</table>

Wadelius M et al. Common VKORC1 and GGCX polymorphisms associated with warfarin dose. Pharmacogenomics Journal 2005; 5: 262-70

On September 17th 2007, the FDA cleared for marketing a genetic test manufactured by Nanosphere Inc.

“The Nanosphere test is not designed to be a stand-alone tool to determine optimum drug dosing, but should be used along with clinical evaluation and other tools, including INR [International Normalized Ratio] to determine the best treatment for patients.”
GWAS and genetic determinants of warfarin dose

- GWAS has confirmed role for CYP2C9 & VKORC1 but also revealed that CYP4F2 also helps to predict dose variance
- CYP4F2 is a vitamin K oxidase
  - Mutation in CYP4F2
  - => ↓ oxidation of vitamin K1
  - => ↑ hepatic levels of vitamin K1
  - => ↑ warfarin dose to achieve anticoagulation

“Large clinical trials have been unable to demonstrate any real advantage of using genotype data for predicting doses and achieving target concentrations so I usually try to downplay the genotype side of warfarin clinical pharmacology.”

Genotype does not completely predict phenotype

23andMe Genetic Health Risk Reports: What you should know

[Image of a 23andMe genetic health risk report]

https://www.23andme.com/test-info/
Table 1: Pharmacokinetics of vitamin K1 and vitamin K1, 2-epoxide in healthy volunteers at steady state with low-dose (2 mg or 0.2 mg orally), after a single dose of vitamin K1 (20 mg orally).

<table>
<thead>
<tr>
<th>Vitamin K1</th>
<th>2-epoxide</th>
<th>Phenoxyparoxysmal (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form</td>
<td>Cmax (ng/ml)</td>
<td>Tmax (h)</td>
</tr>
<tr>
<td>IC</td>
<td>2.04</td>
<td>110</td>
</tr>
<tr>
<td>PW</td>
<td>1.63</td>
<td>107</td>
</tr>
<tr>
<td>RE</td>
<td>0.96</td>
<td>60</td>
</tr>
<tr>
<td>SJ</td>
<td>1.49</td>
<td>50</td>
</tr>
<tr>
<td>GP</td>
<td>1.46</td>
<td>106</td>
</tr>
<tr>
<td>JB</td>
<td>1.47</td>
<td>104</td>
</tr>
<tr>
<td>JF</td>
<td>1.70</td>
<td>105</td>
</tr>
<tr>
<td>ML</td>
<td>2.07</td>
<td>109</td>
</tr>
<tr>
<td>MW</td>
<td>2.08</td>
<td>62</td>
</tr>
<tr>
<td>0.2 mg</td>
<td>1.47</td>
<td>200</td>
</tr>
</tbody>
</table>
“Guangda Ma and I have reported that NextDose with its theory-based model performs better than TCIworks with its empirical model using the same evaluation data set used by the Otago group https://www.page-meeting.org/default.asp?abstract=8562. Guangda did this work as part of his Masters Dissertation last year. Guangda’s PhD proposal is to undertake a clinical trial with NextDose to see if it can be shown to improve outcome compared to standard of care.”

Warfarin and NextDose

- Theory-based modelling of pharmacokinetics and pharmacodynamics of S- and R-warfarin on INR included CYP2C9, VKORC1 and CYP4F2 as well as age, sex body mass and height
  - Fat-free mass was the best predictor of body size influencing CL and V
  - Nick Holford has incorporated this into NextDose (https://www.nextdose.org/), a Bayesian dose forecaster

“Anybody beginning a course of warfarin medicine is advised to keep the vitamin K content of their diet constant. If the warfarin dose is established with a constant level of vitamin K intake the INR will not be affected. Problems may arise when vitamin K intakes are varied. If a patient suddenly lowers their vitamin K intake, the INR will increase, and if a patient increases their vitamin K intake the INR will decrease.”
Warfarin Activity and Diet

- Food sources of vitamin K include:
  - green and/or leafy vegetables, e.g. broccoli, spinach, Brussels sprouts, cabbage & lettuce
  - soybean and canola oil, spirulina, green tea, wheatgerm, alfalfa
  - Beef liver
- Dietary supplements may also contain vitamin K
  - E.g. multivitamins and bone health supplements
  - some milk and health drinks fortified with vitamin K

Penicillins

- The most common reactions to oral penicillin are nausea, vomiting, epigastric distress, diarrhoea, and black, hairy tongue.
- Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy, and nephropathy are infrequent reactions and are usually associated with high doses of parenteral penicillin.
- Hypersensitivity reactions include:
  - skin eruptions (ranging from maculopapular to exfoliative dermatitis);
  - urticaria;
  - reactions resembling serum sickness, including chills, fever, edema, arthralgia, and prostration;
  - laryngeal edema
  - anaphylaxis.

We understand the chemistry, but not inter-individual susceptibility!
Polypharmacy

- Polypharmacy coined as a term to refer to taking several medicines at the same time
  - Generally refers to 4 or 5+ medicines per day
  - Associated with increased risks of adverse drug reactions, adverse drug events, inappropriate prescribing, inappropriate drug use, falls, hospitalization, institutionalization, mortality, and other important negative outcomes in studies of older adults
- Hyperpolypharmacy coined more recently refers to 10 or more medicines
- Has given rise to the concept of deprescribing
  - Rational withdrawal of medications may be the appropriate clinical decision and may result in significant clinical and functional benefits

Table 1 Polypharmacy

<table>
<thead>
<tr>
<th>Percentage of patients on different numbers of regular medications</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4+</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>56.2</td>
<td>26.3</td>
<td>13.9</td>
<td>5.8</td>
<td>4.6</td>
</tr>
<tr>
<td>Gender</td>
<td>86.4</td>
<td>26.3</td>
<td>13.9</td>
<td>4.8</td>
<td>5.2</td>
</tr>
<tr>
<td>Male</td>
<td>61.2</td>
<td>26.3</td>
<td>13.9</td>
<td>5.2</td>
<td>4.6</td>
</tr>
<tr>
<td>Age band</td>
<td>71.7</td>
<td>18.3</td>
<td>3.9</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>60-79</td>
<td>60.2</td>
<td>21.3</td>
<td>11.2</td>
<td>3.1</td>
<td>2.1</td>
</tr>
<tr>
<td>70-79</td>
<td>26.8</td>
<td>20.8</td>
<td>22.2</td>
<td>12.7</td>
<td>9.5</td>
</tr>
</tbody>
</table>

Scottish Index of Multiple Deprivation
catagories
- 1 = least deprived
- 2
- 3
- 4
- 5
- 6

Number of chronic conditions
- 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10 or more

Figure 1

Polypharmacy and hospitalizations

<table>
<thead>
<tr>
<th>Number of clinical conditions</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4+</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>50.0</td>
<td>25.0</td>
<td>25.0</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>1 or 2</td>
<td>50.0</td>
<td>25.0</td>
<td>25.0</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>3 or 4</td>
<td>50.0</td>
<td>25.0</td>
<td>25.0</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>5 or 6</td>
<td>50.0</td>
<td>25.0</td>
<td>25.0</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>7 or more</td>
<td>50.0</td>
<td>25.0</td>
<td>25.0</td>
<td>5.0</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2

Adjusted odds ratio showing the association between number of regular medications (per 1 regular medication) and all-cause hospitalizations for different levels of polypharmacy (polypharmacy index categories). The hospitalization rate ratio was calculated for each level of polypharmacy as a separate variable using the ordinary least squares regression. The Wald test and Chi-square test can be calculated from the adjusted odds ratios reported in Appendix 2.
Pharmacokinetic Interactions

• Inhibition
  – results in higher than expected plasma concentrations so pharmacology is exaggerated
  – Inhibition of one pathway results in a greater clearance through the bioactivation pathway
  – Inhibition of detoxification pathways or repair mechanisms
• Induction
  – Enhanced bioactivation may increase incidence of ADR
  – Enhanced metabolic clearance: decreased clinical effectiveness

Pharmacodynamic Interactions

• Adverse drug reactions may be due to a pharmacodynamic interaction between 2 or more drugs, so that the pharmacological effect is too great
• Ethanol has many pharmacological effects, including acting at GABA_A receptors
• Drinking alcohol with sedatives, hypnotics and some antihistamines can result in additive or synergistic effects
• Outcome is too much sedation or coma and death

Anna Nicole Smith:
A Pharmacology Basket Case

• Chloral hydrate
  – Hypnotic used for short-term treatment of insomnia or sedative before minor surgery
  – Has activity at GABA_A
• Diphenhydramine
  – 1st Generation antihistamine with sedative & anti-tussive effects
  – Central H_1 effects causes drowsiness but also antagonist at muscarinic receptors and it is a serotonin reuptake inhibitor
• Clonazepam/diazepam/nordiazepam/temazepam/oxazepam/lorazepam
  – Anxiolytics/hypnotics working through GABA_A
• Topiramate
  – Anticonvulsant but also has some GABA_A activity