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).

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.

ADR Incidence

- ADR are a large problem: ~ 5% of hospital admissions are as a result of an ADR.
- Once in hospital, the scope for ADR increases dramatically.
- The FDA receives ~250,000 reports of ADR/year
  - Estimated cost of $75 billion annually
  - Among top 10 leading causes of 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.


ADR –Dependent Hospital Admissions in the UK

- **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 (£706m, €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.

ADR in New Zealand: 1974-1994 Experience

- 22455 Reports of Adverse drug reactions
  - 417 deaths (1.9% mortality rate)
- 943 Reports (4.2% of total) involved the liver
  - 31 deaths (3.3% mortality)
  - 7.4% of total mortality
- 205 Drugs associated with hepatic reactions
- 61% of all ADR & 57% of hepatic ADR were in female


Hepatotoxicity in NZ over 21 years

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency a</th>
<th>Functional Abnorm.</th>
<th>Hepatic Necrosis</th>
<th>Hepatic Cholestasis</th>
<th>Jaundice</th>
<th>Other</th>
<th>Deaths</th>
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<tr>
<td>Erythromycin*</td>
<td>109</td>
<td>27</td>
<td>9</td>
<td>22</td>
<td>33</td>
<td>9</td>
<td>2</td>
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<tr>
<td>Halothane</td>
<td>64</td>
<td>23</td>
<td>24</td>
<td>8</td>
<td>32</td>
<td>13</td>
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<tr>
<td>Perhexiline (PEXSIG )</td>
<td>43</td>
<td>84</td>
<td>5</td>
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<td>38</td>
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<td>2</td>
<td>0</td>
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<td>58</td>
<td>0</td>
<td>16</td>
<td>18</td>
<td>8</td>
<td>0</td>
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<tr>
<td>Methyldopa</td>
<td>33</td>
<td>62</td>
<td>9</td>
<td>9</td>
<td>11</td>
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<td>Augmentin</td>
<td>32</td>
<td>22</td>
<td>14</td>
<td>22</td>
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<td>Cotrimoxazole‡</td>
<td>29</td>
<td>31</td>
<td>0</td>
<td>19</td>
<td>41</td>
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<td>1</td>
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<td>Chlorpromazine</td>
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<td>14</td>
<td>0</td>
<td>34</td>
<td>38</td>
<td>14</td>
<td>1</td>
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</tbody>
</table>

*Often associated with other antibacterial therapy
‡ Also complications with neurological damage

ADR Mechanisms

The mechanisms involved may vary widely, but involves:
- Interaction with receptor or enzymes (pharmacological?)
  - Type I. Predictable, dose-dependent based on the known pharmacology of the drug
  - Type II. Not predictable, no clear dose-dependency and not due to the known pharmacology of the drug

Figure 1

Classification of adverse drug reactions; these adverse drug reactions are divided according to their on-target or off-target interactions between the drug and cellular components. Both on-target and off-target effects can be immunologically complex, often involving the pharmacological action of a drug and its immunomodulatory properties. On-target reactions generally refer to an immunological action of a drug and off-target effects can occur by both immune mediated and non-immune mediated mechanisms described from White et al. (72)

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

Preventing ADR

'Safety Pharmacology'

Fig. 1 Objectives of safety pharmacology studies and their alignment to the drug discovery and development process. Abbreviation: Nb cpds, approximate number of compounds evaluated for each discovery/development phase; FTIM, First Time In Man.
The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH):

**Safety Guidelines**

- CARCINOGENICITY STUDIES
  - S1A Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals
  - S1B Testing for Carcinogenicity of Pharmaceuticals
  - S1C(R2) Dose Selection for Carcinogenicity Studies of Pharmaceuticals
- GENOTOXICITY
  - S2(R2) Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use (this guideline replaces and combines S2A and S2B)
- TOXICOGENETICS AND PHARMACOKINETICS
  - S3A Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies
  - S3B Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies
- TOXICITY TESTING
  - S4 Duration of Chronic Toxicity Testing in Animals (Rodent and Non-Rodent Toxicity Testing)
- REPRODUCTIVE TOXICITY
  - S5(R2) Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility
- BIOTECHNOLOGICAL PRODUCTS
  - S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
- PHARMACOLOGY STUDIES
  - S7A Safety Pharmacology Studies for Human Pharmaceuticals
  - S7B The Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals
- IMMUNOTOXICOLOGY STUDIES
  - S8 Immunotoxicity Studies for Human Pharmaceuticals
  - S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

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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
    - E1A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
  - E2(R2) Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports
  - E2(C) Clinical Pharmacokinetics: Definition, Standards and Standards for Expedited Reporting
  - E2(E) Pharmacovigilance Planning
  - E2(F) 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 Good Clinical Practice: Consolidated Guideline

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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 suitable models for many human ADRs (e.g. hypersensitivity reactions)
Clinical Volunteers and TGN 1412
March 13 2006.

- 8 Men took part in a phase I trial for a monoclonal antibody TGN1412
  - immunomodulatory humanized agonistic anti-CD28 monoclonal antibody
  - developed for the treatment of immunological diseases, e.g.
    multiple sclerosis, rheumatoid arthritis and certain cancers

<table>
<thead>
<tr>
<th>Subjects</th>
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<th>2</th>
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<th>4</th>
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<td>69.9</td>
<td>69.5</td>
<td>82.4</td>
<td>82.1</td>
<td>51.8</td>
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<tr>
<td>Dosing</td>
<td>TGN1412</td>
<td>8.6 mg</td>
<td>6.5 mg</td>
<td>8.6 mg</td>
<td>3.2 mg</td>
<td>7.2 mg</td>
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<td>08:20</td>
<td>08:19</td>
<td>04:19</td>
<td>04:19</td>
<td>04:19</td>
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</tbody>
</table>

Symptoms and timing

A number of symptoms were reported by the subjects fairly soon after administration of the investigational agent (drug placebo).

- In 5 of 6 subjects, headache was reported between 59-90 minutes.
- All reported nausea.
- Rigors were reported between 58-120 minutes in 4 subjects.
- Elevated temperatures >38°C were noted between 2.5 to 6.5 hours.
- Hypotension was noted between 3.5 to 4.6 hours after administration.
- Tachycardia noted at 2.5 to 4.6 hours.

Transfer to Critical Care

All 6 symptomatic subjects were transferred to the Critical Care Unit at Northwick Park hospital between 12 and 16 hours after dosing in view of the continued deterioration in clinical status.

On transfer to critical care unit, the following were the predominant and common features: dyspnoea and tachypnoea in 5 of the 6; respiratory failure in 4 of the 6; bilateral radiological pulmonary infiltrates in all; increased blood urea, significant base deficit, and features consistent with disseminated intravascular coagulation (elevated fibrinogen degradation products (FDP), low fibrinogen and altered prothrombin time). There was general lymphopenia (values ranging between 0.64 to 9.07 x 10^9/L). There was a fall in lymphocytes compared to pre-dose baseline 1.47 to 2.92 x 10^9/L and this persisted for several days.

Treatment in Critical Care

- Ventilation:
  - All subjects (patients) needed assisted ventilation: 4 of the 6 non-surviving patients received continuous positive pressure ventilation (CPAP) for durations of 4-42 hours.
  - Interim positive pressure ventilation (IPPV) was initiated in two subjects (12-16 hours post dose).
  - Two patients needed IPPV.

Cytokine table

<table>
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<tr>
<th></th>
<th>PHASE 1</th>
<th>1 DOSE</th>
<th>4 HOURS</th>
<th>DAY 2</th>
<th>DAY 4</th>
<th>DAY 5</th>
<th>DAY 7</th>
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<tr>
<td>Mean 48h</td>
<td>2.8</td>
<td>14.3</td>
<td>7.6</td>
<td>110</td>
<td>158</td>
<td>126</td>
<td>73</td>
<td>5.9</td>
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<tr>
<td>Mean 4h</td>
<td>1.1</td>
<td>8.0</td>
<td>5.8</td>
<td>47.0</td>
<td>148</td>
<td>275</td>
<td>88</td>
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<tr>
<td>Mean 12h</td>
<td>1.9</td>
<td>9.1</td>
<td>7.1</td>
<td>47.5</td>
<td>147</td>
<td>273</td>
<td>89</td>
<td>6.3</td>
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<tr>
<td>Mean 36h</td>
<td>1.8</td>
<td>9.7</td>
<td>7.1</td>
<td>47.5</td>
<td>147</td>
<td>273</td>
<td>89</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Cytokine concentrations in human plasma and serum are shown. All cytokines increased significantly on day 2 and 3. Very large increases (>500-5000 pg/mL) were seen in TNF and interleukins gamma and especially on day 4 and day 7. Interestingly, TNF rose sharply in all subjects within 1 hour of TGN1412 administration. A downward trend was seen in all cytokines on day 4 after administration.

Conclusion

The investigations indicated that the adverse incident did not involve errors in the manufacture of TGN1412 or in its formulation, dilution or administration to trial participants. It was, therefore, concluded that an unpredicted biological action of the drug in humans was the most likely cause of the adverse reactions in the trial participants.
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

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 TNFα 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


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

In the ill-fated FIH trial of TGN1412 in 2006, healthy volunteers (HV) 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

Causes Of Attrition During Drug Development

- ADME: 39%
- Lack of Efficacy: 10%
- Animal Toxicity: 11%
- ADR in Humans: 5%
- Commercial Reasons: 3%
- Misc.

Guengerich FP, MacDonald JS. Applying mechanisms of chemical toxicity to predict drug safety. Chem Res Toxicol 2007;20:344-69

**ADR: Time and Type**

- Many serious ADR are only discovered after the drug has been on the market for a number of years
  - ~50% of all drug withdrawals occur within the first 2 years
  - Only ~50% of serious ADR are detected and documented in Physicians’ Desk Diary within 7 years after approval
- Of the ~20 drugs withdrawn from the US market between 1975-2000, most were due to hepatotoxicity, blood dyscrasias and drug interactions, often cardiotoxicity.
COX-2 Inhibitors: Vioxx

• MERCK & CO withdrew rofecoxib (Vioxx) from the market on September 30, 2004, based on unpublished data from their own APPROVe trial
• 1 Year after the drug’s approval, the VIGOR [Vioxx Gastrointestinal Outcomes Research Study] trial demonstrated a 4-fold increased risk of acute myocardial infarction with once-daily 50-mg doses of rofecoxib compared with twice-daily 500-mg doses of naproxen among patients with rheumatoid arthritis

And for the people that died…

• It has been estimated that Vioxx could have caused 27,785 heart attacks or deaths since it was approved for use in 1999
  – More than 4,200 lawsuits have been filed against the firm over the drug
• August 19, 2005: A Texas jury found Merck & Co liable for the death of a man who took Vioxx
  – Jurors rejected Merck’s argument that Robert Ernst, 59, died of clogged arteries rather than a Vioxx-induced heart attack that led to his fatal arrhythmia.
  – Ernst ran marathons and taught aerobics classes
  – Awarded US $253.4 million in damages to his widow (later reduced to $26 million)
• November 9, 2007, Merck agreed to pay $4.85 billion to settle nearly 27,000 lawsuits although specifying that Merck “does not admit causation or fault”

"You've got to fine Merck and all Merck knows is money. You have got a company worth billions and billions and billions of dollars - how do you fine them?
"If you write down $10m, Merck laughs. It's a rounding error. It's got to be over $100m or they won't even pay attention."

Mark Lanier, lawyer for Mrs Ernst

COX-2 Inhibitors

"Several lessons can be learned from the 5-year experience and eventual withdrawal of rofecoxib from the market. First, the current postmarketing surveillance system does not work. If the FDA is to continue to approve drugs rapidly, we should not expect that all safety issues will be understood prior to a drug’s approval," Drs. Solomon and Avorn write.

"The agency will need to be more effective in requiring specially designed premarketing clinical safety trials when phase II or small phase III trials suggest reason for specific concerns. Such a system should be rapidly responsive and objective, and safeguards to protect this agenda against industry influence must be put in place."

• Authors warn against assuming a class effect when evaluating a drug’s safety, as exemplified by cerivastatin, troglitazone, and bromfenac, each of which was withdrawn from the market not long after approval because of liver toxicity or other adverse effects.
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

Source: W.K. Why there is a need for pharmacovigilance. Pharmacoepidemiology and Drug Safety 1999;8:61-4

Overview of activities undertaken by the NZ Pharmacovigilance Centre (NZPhvC)

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, PEKSBG should not be prescribed.

MINUTES OF THE 152ND MEDICINES ADVERSE REACTIONS COMMITTEE MEETING

13 December 2012

Key Messages

- 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 Māori 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, extreme sleepiness, difficulty waking, confusion, shallow breathing and coma. 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


Ethical Considerations

Genetics and Susceptibility to Toxic Chemicals: Do You (or Should You) Know Your Genetic Profile?

LARRINDA M. LARSON, RONALD N. HINES, FRANK J. GONZALEZ, TIMOTHY P. ZACHARIEVESKI, and MARK A. ROTHEMUTH

Department of Pharmacology, Wayne State University College of Medicine, Detroit, Michigan 48201-1808. Departments of Pediatrics and Pharmacology/Toxicology, Medical College of Wisconsin, Milwaukee, Wisconsin 53205; Laboratory of Pharmacology, National Cancer Institute, Bethesda, Maryland 20892; Department of Toxicology and Environmental Biology, National Food Safety and Toxicology Center, Michigan State University, East Lansing, Michigan 48824; and Institute for Biospheric Health Policy and Law, University of Louisville School of Medicine, Louisville, Kentucky 40292.

Received October 13, 2003; accepted January 20, 2004.
HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin

Table 1: Distribution of HLA-B*5701 genotypes

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative</th>
<th>P-value</th>
<th>OR</th>
<th>95% CI</th>
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<td>Control  (n = 40)</td>
<td>4 (10.0)</td>
<td>36 (90.0)</td>
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<tr>
<td>Cases (n = 50)</td>
<td>14 (28.0)</td>
<td>36 (72.0)</td>
<td>8.67 × 10⁻²³</td>
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</table>

Replication cases were those exposed to a semisynthetic carbapenem with flucloxacillin in —7 all flucloxacillin DILI cases occurred after the 39th day (t = 19). Percentages are given as parentheses. P-values are given in parentheses.

- ~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 (6TGN) and more of 6MMP which may be hepatotoxic

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/8x10⁸ RBC
  - 6-MMP <5700 pmol/8x10⁸ RBC
- Very poor correlation between AZA dose and 6-TGN concentration (r² = 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

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**Warfarin**

- In a study into the effects of excessive anticoagulation on morbidity and mortality:
  - Major bleeding occurring during administration of warfarin and other anticoagulants
  - 50% of patients had excessive anticoagulation.
- Excessive warfarin therapy associated with an increased 60-day mortality ($P = 0.049$)
  - Excessive anticoagulation a significant predictor of nonfatal end points of stroke, myocardial infarction, hypotension, critical anemia and surgical or angiographic intervention at 30 days (HR, 2.17; 95% CI, 1.25-3.78; $P = 0.006$)


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**Vitamin K Cycle**

- Vitamin K Reductase
- Vitamin K Epoxide Reductase
- Prothrombin
- Prothrombin Precursor (Factor II)
- Prothrombin Precursor (Factor II)
- Vitamin K Hydroquinone
- Vitamin K Epoxide

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- Vitamin K Reductase
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- Prothrombin Precursor (Factor II)
- Vitamin K Hydroquinone
- Vitamin K Epoxide

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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 requirement.
  - “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%</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>


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.”

http://www.fda.gov/cder/foi/foixsum/1999fdaarth/1999fdaarth08.htm

“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 and Hospitalization**

- 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

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**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
Clozapine & Smoking

- An atypical antipsychotic metabolised by CYP1A2
  - Differences in CYP1A2 activity account for ~70% of variance in [plasma]
  - Smoking ↑CYP1A2 => ↑ metabolic clearance => ↑ [plasma]
- Doses of clozapine titrated at initiation of therapy:
  - if patient stops smoking: ↓CYP1A2 => ↓ metabolic clearance => ↓ [plasma]
  - Can lead to sedation, fatigue, seizure
- Needs to be considered if patient starts smoking cessation therapy (e.g. varenicline, bupropion)
  - Clozapine level after smoking cessation (ng/mL) = 45.3 + 1.474 [Baseline clozapine level](ng/mL)
  - Admission to a smoke-free hospital may a problem!


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 act GABA<sub>A</sub> 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<sub>A</sub>

- Diphenhydramine
  - 1st Generation antihistamine with sedative & anti-tussive effects
  - Central H<sub>1</sub> 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<sub>A</sub>

- Topiramate
  - Anticonvulsant but also has some GABA<sub>A</sub> activity