Drug Safety

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The Burden of Adverse Drug Reactions

Admission (6.5%)

In patients (14.7%)

Emergency Room (2.5%)

Primary Care (25%)

Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients
Maike Pocklington, Sally James, Khone Moua, Chris Green, Andrew R. Scott, Thomas J. Walker, Keith Burton, A. Kevin Firk, Amanda W. Bednarsek

Adverse Drug Reactions in Hospital In-Patients: A Prospective Analysis of 3693 Patient-Episodes
Sama C. Denke1, Christopher P. Green2, Stephen Taylor3, Peter A. Williams2, David R. Mattson2, Martin Perriello1

National Surveillance of Emergency Department Visits for Outpatient Adverse Drug Events

Patient Safety

Adverse Drug Events in Ambulatory Care
<table>
<thead>
<tr>
<th>Drug substance ( Brand name )</th>
<th>Year action taken</th>
<th>Major safety concerns</th>
<th>Licence Holder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilevalol (Unicard)</td>
<td>1990</td>
<td>Hepatotoxicity</td>
<td>Schering – Plough Limited</td>
</tr>
<tr>
<td>Metipranolol (Glauline eye drops 0.6%)</td>
<td>1990</td>
<td>Uveitis</td>
<td>Chauvin Pharmaceuticals</td>
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<tr>
<td>Triazolam (Halcion)</td>
<td>1991</td>
<td>Psychiatric reactions</td>
<td>Upjohn</td>
</tr>
<tr>
<td>Terodiline (Micturin)</td>
<td>1991</td>
<td>Arrhythmias</td>
<td>Pharmacia</td>
</tr>
<tr>
<td>Temafloxacin (Teflox)</td>
<td>1992</td>
<td>Multi-system toxicity</td>
<td>Abbott Labs</td>
</tr>
<tr>
<td>Flosequinan (Manoplax)</td>
<td>1993</td>
<td>Excess mortality</td>
<td>Boots</td>
</tr>
<tr>
<td>Remoxipride (Roxiam)</td>
<td>1994</td>
<td>Aplastic anaemia</td>
<td>Astra</td>
</tr>
<tr>
<td>Naftidrofuryl Oxalate Injection (Praxilene)</td>
<td>1995</td>
<td>Cardiotoxicity</td>
<td>Lipha</td>
</tr>
<tr>
<td>Pemoline (Volital)</td>
<td>1997</td>
<td>Hepatotoxicity</td>
<td>Various companies</td>
</tr>
<tr>
<td>Troglitazone (Romazin)</td>
<td>1997</td>
<td>Hepatotoxicity</td>
<td>Glaxo Wellcome</td>
</tr>
<tr>
<td>Sertindole (Serdolect)</td>
<td>1998*</td>
<td>Arrhythmias</td>
<td>Lundbeck A/S</td>
</tr>
<tr>
<td>Tolcapone (Tasmar)</td>
<td>1998</td>
<td>Hepatotoxicity</td>
<td>Roche</td>
</tr>
<tr>
<td>Fenfluramine (Ponderax)</td>
<td>1998</td>
<td>Cardiac valvular disease</td>
<td>Servier</td>
</tr>
<tr>
<td>Mibefradil (Posicor)</td>
<td>1998</td>
<td>Drug interactions</td>
<td>Roche</td>
</tr>
<tr>
<td>Trovafloxacin (Trovan)</td>
<td>1999</td>
<td>Hepatotoxicity</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Grepaflloxacin (Raxar)</td>
<td>1999</td>
<td>QT prolongation</td>
<td>Glaxo Wellcome</td>
</tr>
<tr>
<td>Pulmonary surfactant (Alec)</td>
<td>2000</td>
<td>Increased mortality</td>
<td>Britannia Pharmaceuticals Ltd</td>
</tr>
<tr>
<td>Cisapride (Prepulsid, Alimix)</td>
<td>2000</td>
<td>Disorders of heart rhythm</td>
<td>Janssen-Cilag</td>
</tr>
<tr>
<td>Droperidol (Droleptan)</td>
<td>2001</td>
<td>Disorders of heart rhythm</td>
<td>Janssen-Cilag</td>
</tr>
<tr>
<td>Cerivastatin (Lipobay)</td>
<td>2001</td>
<td>Rhabdomyolysis</td>
<td>Bayer</td>
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<tr>
<td>Rofecoxib (Vioxx)</td>
<td>2004</td>
<td>Risk of thrombotic events</td>
<td>Merck Sharp &amp; Dohme</td>
</tr>
<tr>
<td>Valdecoxib (Bextra)</td>
<td>2005</td>
<td>Serious skin reactions</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Co-proxamol (paracetamol + dextropropoxyphene)</td>
<td>2005</td>
<td>Risks of overdose and misuse</td>
<td>various</td>
</tr>
</tbody>
</table>
Drug Response

\[
\text{Drug Response} = f_1 \left[ \text{Chemistry of drug} \right] + f_2 \left[ \text{Biology of individual} \right]
\]

Tools to understand both \( f_1 \) and \( f_2 \) are becoming increasingly available.
Centr e for Drug Safety Science

Understanding Mechanisms of Adverse Drug Reactions
Mission for the Centre

- To create a world-class centre for the investigation of fundamental mechanisms of clinically important adverse drug reactions with the overall aim of preventing such reactions by improved drug selection and design and more informed patient selection, and the provision of training in drug safety science.
Vision for the Centre

Non-competitive and integrated collaborations between

- Academia
- Research Institutions
- Regulatory Agencies
- Government
- Industry

Collaboration with IDSS (Paul Watkins)
Expected Outcome - Closing The Loop

"Closing the loop" on adverse drug reactions

Define structural basis of liability

Characterize ADR

Identify causal biochemical variable

Characterize patient phenotype/genotype

DRUG
What we aim to deliver

- Inform the clinician
- Inform the patient
- Inform the regulator
- Inform basic and clinical science
- Inform the drug discovery process
- Inform the public what is feasible
Experimental Approaches
Experimental Approaches
Experimental Approaches

Dynamic
Iterative
CDSS and Pharmacogenetics Research


**NEW ENGLAND JOURNAL OF MEDICINE**


**Warfarin pharmacogenetics: a single VKORC1 polymorphism is predictive of dose across 3 racial groups**

**Genotype-guided dosing of clotting drugs:** the European pharmacogenetics of anticoagulant therapy (EU-PACT) trial design. Pharmacogenomics 2009;10(10):1287-95.

**NEW ENGLAND JOURNAL OF MEDICINE**
Regan, Maggs, Hammond et al., 2010

Acyl Glucuronides: The Good, The Bad and The Ugly

Sophie L. Pope1,2, James L. Maggs2, Thomas G. Hammond2, Craig Lambert2, Dominic P. Williams2, and B. Kunze Park2
1MRC Centre for Drug Safety Science, School of Pharmacy, University of Liverpool, Liverpool, UK
2Clinical Pharmacology and Therapeutics, AstraZeneca R&D Charnwood, Marcet Road, Leicestershire LE10 0SB, UK

Antoine et al., 2009, 2010

High-Mobility Group Box-1 Protein and Keratin-16, Circulating Serum Proteins Informative of Acetaminophen-Induced Necrosis and Apoptosis in Vivo

Daniel I. Antoine,1,2 Dominic P. Williams,2 Aruna Kripa,2 Rodwell E. Jenkins,2 Sophie L. Pope1,2, and J. Kevin Park1
1MRC Centre for Drug Safety Science, School of Pharmacy, University of Liverpool, Liverpool, UK
2Clinical Pharmacology and Therapeutics, AstraZeneca R&D Charnwood, Marcet Road, Leicestershire LE10 0SB, UK

Srivastava et al., 2009

Integrated systems for quantifying metabolite biomarkers of hepatic bioactivation in patients

Abhinav Srivastava, Le-Thu Lu, James L. Maggs, Massoud Chapanova, Murali Premkumar, Dominic P. Williams, and B. Kevin Park
MRC Centre for Drug Safety Science, School of Pharmacy and Therapeutics, University of Liverpool, Liverpool, UK

Laverty et al., 2010

The potential of cytokines as safety biomarkers for drug-induced liver injury

Hugh G. Laverty1, Daniel J. Antoine1, Craig Benson2, Masoud Chapanova1, Dominic Williams1, B. Kevin Park1
1MRC Centre for Drug Safety Science, School of Pharmacy and Therapeutics, University of Liverpool, Liverpool, UK
2Clinical Pharmacology and Therapeutics, AstraZeneca R&D Charnwood, Marcet Road, Leicestershire LE10 0SB, UK
Workshops

- Workshops to discuss key areas
- Developed in conjunction with the ABPI
- Involves academics, regulators, Industry and healthcare
- Outputs and recommendations
How can we make a difference?

Training

- MRes in Drug Safety Science
  - 1 year research-based Masters course
  - 3 x 10 week research projects
  - Core lectures in Pharmacology and Drug Safety Science

- PhD in Drug Safety Science
  - 1+3 year, 3 year or 4 year options

- Research Fellows

- Clinical Fellows
The Scheme

MRC Clinical Pharmacology and Therapeutics Fellowships

MRC Centre for Drug Safety Science (A Liverpool-Manchester Collaboration)

Liverpool
- Wolfson Centre for Personalised Medicine
- LiverpoolEPRC and BRI
- Liverpool School of Tropical Medicine

Manchester
- Interdisciplinary Biocentre
- Manchester BRC
- Manchester Academic Health Science Centre

Medicines for Children Research Network

Partnerships
- AstraZeneca, GSK, ICON and MEU

University of Liverpool

The Wolfson Centre for Personalised Medicine

MRC Centre for Drug Safety Science
Case Study

A new genetic biomarker for carbamazepine hypersensitivity in Caucasians
HLA-A*3101 and Carbamazepine-Induced Hypersensitivity Reactions in Europeans

- Conducted in collaboration with Epigen Consortium
- Replication:
  - Epigen consortium
  - Patients from EU
  - Independently by Japanese and South Koreans
- Covers all phenotypes
  - OR 9.12
- Distinct from HLA-B*1502 which is
  - ethnic specific
  - phenotype specific
Next Steps

- What should regulators do about this biomarker?
  - Replicated in at least 3 populations but all from case control analysis
- If drug label is changed, what form should it take?
- What should clinicians do about the biomarker in patients who require CBZ hypersensitivity
  - Number needed to test to prevent one case of CBZ hypersensitivity is 47-67 (cf. HLA-B*1502: NNT is 1819)
- Is there a need for a prospective study for the demonstration of clinical utility?
- How would such a prospective study be funded since the drug is off patent?
Drug regulation must always follow science

The ethos of regulatory science is consistent with this.