Toxicovigilance

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www.sactrc.org

Wellcome Trust & Australian National Health and Medical Research Council
International Collaborative Capacity Building Research Grant (GR071669MA)
Entering the prescription club
Overview

- Toxicovigilance (it sounds like a word someone made up)
- Case reports
- Fatal toxicity indexes
- Relative clinical toxicity (Clinical databases)
- Overcoming current limitations
Toxicovigilance (Descotes)

- “Active detection” - of clinical adverse events
- “Data validation” – review of details by someone with toxicological expertise
- “Specific follow up” – sub-groups (e.g. children)
- “Thus, toxicovigilance can contribute to hazard identification and risk assessment by providing medically validated data which are often overlooked in the process of risk assessment. So far, very few structured toxicovigilance systems have been set up and hopefully national and international initiatives will bridge this gap in our knowledge of the toxicity of many chemicals and commercial products in human beings.”

BRIEF REVIEW

POISONING AND EPIDEMIOLOGY: ‘TOXICOEPIDEMIOLOGY’

Nicholas A Buckley

Discipline of Clinical Pharmacology, University of Newcastle, Newcastle Mater Misericordiae Hospital, Waratah, New South Wales, Australia

SUMMARY

1. There is little hypothesis-testing clinical research performed in toxicology. Randomized clinical trials are rare and most observational studies are performed on highly selected patients and are subject to marked bias. Thus, for many poisonings, our approach has been based almost entirely on deduction from known pharmacological/toxicological effects, generalizations from drugs within the same therapeutic class, animal data and case reports. This is also far from satisfactory, as many toxicological mechanisms are poorly understood and not related to the therapeutic class.

Key words: clinical research, Cochrane Collaboration, epidemiology, evidence-based, poisoning.

‘Each victim of suicide gives his act a personal stamp which expresses his temperament, the special conditions in which he is involved and which, consequently, cannot be explained by the social and general causes of the phenomenon.’

Émile Durkheim (1858–1917)

INTRODUCTION

...
Eternal vigilance is the price of liberty; power is ever stealing from the many to the few.  
**Wendell Phillips**

I sometimes think that the price of liberty is not so much eternal vigilance as eternal dirt.  
**George Orwell**
Eternal vigilance is the price of liberty; power is ever stealing from the many to the few.

Wendell Phillips

I sometimes think that the price of liberty is not so much eternal vigilance as eternal inert.

George Orwell

CASE REPORTS

DATA MINING
Case reports – the key is clinical recognition and lab confirmation
Good example of the power (or failure) of toxicovigilance?

Mattel issues new massive China toy recall
About 9 million items recalled; danger from magnets and lead paint

Toy-making giant Mattel issued a recall for about 9 million Chinese-made toys, including Polly Pocket dolls, shown here.
γ-Hydroxybutyrate poisoning from toy beads

Naren Gunja, Evelyn Doyle, Kevin Carpenter, Olivia T Chan, Simon Gilmore, Gary Browne and Andis Graudins

A 2-year-old boy and a 10-year-old girl presented to the emergency department with a decreased level of consciousness. The girl had had persistent vomiting and a seizure. Urine metabolic screening tests were positive for γ-hydroxybutyrate (GHB). Samples from toy beads ingested by both children contained 1,4-butanediol, which is metabolised to GHB in humans. Regulatory authorities were notified, leading to an international recall of the toy beads. (MJA 2008; 188: 54-55)
Police warn of deadly ecstasy threat

Police are warning people in south-east South Australia to be wary of a new, more dangerous type of ecstasy pill making its way through the region.

Police say all forms of ecstasy are dangerous, but the new type marked with a wheelchair puts users at a higher risk of severe illness.

Associate Professor Rod Irvine from the University of Adelaide's School of Pharmacology says these types of pills are often made with cheaper ingredients and using them can have severe consequences.

"It can kill you, I mean it's as simple as that," he said.

"There's been quite a few people in South Australia, not so much in recent years, but a few years ago, who have died from taking what they thought were ecstasy tablets they'd taken them on many occasions before," he said.
Toxic canisters wash up on Queensland beaches

January 2, 2013

Police are warning people not to handle mysterious silver canisters containing a toxic gas that are washing up on beaches in central Queensland.

The silver canisters, which have been found on beaches since February last year, contain toxic aluminium phosphide which can be fatal if inhaled or ingested.

Aluminium phosphide is a colourless, flammable and toxic gas.

Mild exposure by inhalation can cause a ringing in the ears, fatigue, nausea and pressure in the chest.

Police have received reports of the containers being found between Lady Elliot Island and Mabuiag Island, with the most recent being discovered at Zilzie near Rockhampton.
Overview

- Toxicovigilance
- Case reports

Fatal toxicity indexes
- Relative clinical toxicity (Clinical databases)
- Overcoming current limitations?
  - Poisons centre network
  - Toxicovigilance laboratory
Beyond case-reports - toxicoepidemiology

- Justifying interventions might benefit from “Relative toxicity” data
- Fatal toxicity indices (deaths/?????????)
- Relative frequency (poisoning/????????)
- Relative clinical toxicity (???????/poisoning)
  - PIC Calls
  - Clinical databases
HYPNOTICS AND SEDATIVES: AN INDEX OF FATAL TOXICITY

Sir,—In 1974, Girdwood\textsuperscript{3} suggested that the fatal toxicity of specific drugs could be determined by the ratio of the number of deaths reported annually to the number of prescriptions (millions) per year (R/M). That study was confined to deaths reported to the Committee on Safety of Drugs; deaths from an overdose of established drugs were largely excluded.

We have now extended this work to include all deaths associated with a particular drug. The hypothesis is presented that the mortality rate associated with certain types of drug is determined only by the intrinsic toxicity of the drug and the number of individuals with access to it.

The index R/M, as given above, is now re-defined as T to include all drug-associated deaths in a three year period, and is normalised to T (quinalbarbitone) = 100. The absolute death rate for quinalbarbitone in the period 1976–78 was 698 per million prescriptions.
<table>
<thead>
<tr>
<th>Drug</th>
<th>T</th>
<th>Drug</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinalbarbitone</td>
<td>100</td>
<td>Glutethimide</td>
<td>16.4</td>
</tr>
<tr>
<td>Chlormethiazole</td>
<td>79.6*</td>
<td>Butobarbitone</td>
<td>15.1</td>
</tr>
<tr>
<td>Pentobarbitone</td>
<td>65.8</td>
<td>Methaqualone</td>
<td>15.1†</td>
</tr>
<tr>
<td>Amylobarbitone</td>
<td>59.2</td>
<td>Flurazepam</td>
<td>6.8</td>
</tr>
<tr>
<td>Carbromal</td>
<td>38.2</td>
<td>Phenobarbitone</td>
<td>5.7</td>
</tr>
<tr>
<td>Chloral + dichloralphenazone</td>
<td>19.8</td>
<td>Meprobamate</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nitrazepam</td>
<td>1.5</td>
</tr>
</tbody>
</table>

* 1977 + 1978 only. † 1976 + 1977 only.
Relation between the index of fatal toxicity (T) and the n-octanol/water partition coefficient (P) for five barbiturates.

Straight line shows the least squares fit \( r = 0.992; p < 0.001 \). 1 = phenobarbitone; 2 = butobarbitone; 3 = pentobarbitone; 4 = amylobarbitone; 5 = quinalbarbitone.
TABLE II—Fatal poisoning, prescription data, and fatal toxicity indices 1975-84 for antidepressant drugs in England, Wales, and Scotland

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year introduced</th>
<th>Fatal poisonings</th>
<th>Fatal toxicity indices</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No observed</td>
<td>No expected</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dibenzepin</td>
<td>1970</td>
<td>4</td>
<td>0.9</td>
</tr>
<tr>
<td>Desipramine</td>
<td>1963</td>
<td>13</td>
<td>5.7</td>
</tr>
<tr>
<td>Dothiepin</td>
<td>1969</td>
<td>533</td>
<td>372</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>1961</td>
<td>1181</td>
<td>886</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>1963</td>
<td>57</td>
<td>51</td>
</tr>
<tr>
<td>Doxepin</td>
<td>1969</td>
<td>102</td>
<td>114</td>
</tr>
<tr>
<td>Imipramine</td>
<td>1959</td>
<td>278</td>
<td>342</td>
</tr>
<tr>
<td>Trimipramine</td>
<td>1966</td>
<td>155</td>
<td>196</td>
</tr>
<tr>
<td>Opipramol</td>
<td>1963</td>
<td>2</td>
<td>3.2</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>1970</td>
<td>51</td>
<td>160</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>1966</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>Iprindole</td>
<td>1967</td>
<td>2</td>
<td>8.9</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>1960</td>
<td>15</td>
<td>9.0</td>
</tr>
<tr>
<td>Phenelzine</td>
<td>1959</td>
<td>24</td>
<td>36.7</td>
</tr>
<tr>
<td>Isocarboxazid</td>
<td>1960</td>
<td>3</td>
<td>8.2</td>
</tr>
<tr>
<td>Iproniazid</td>
<td>1958</td>
<td>0</td>
<td>0.97</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>1960</td>
<td>15</td>
<td>9.0</td>
</tr>
<tr>
<td>Phenelzine</td>
<td>1959</td>
<td>24</td>
<td>36.7</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>1960</td>
<td>3</td>
<td>8.2</td>
</tr>
<tr>
<td>Iproniazid</td>
<td>1958</td>
<td>0</td>
<td>0.97</td>
</tr>
</tbody>
</table>

*Significantly different at 5% level from all antidepressants (p<0.05).
**Significantly different at 1% level from all antidepressants (p<0.01).
***Significantly different at 0.1% level from all antidepressants (p<0.001).
Fatal toxicity index (deaths per million prescriptions) for antidepressants ranked within British National Formulary classes

<table>
<thead>
<tr>
<th>Drug</th>
<th>No of prescriptions (thousands)</th>
<th>Total deaths</th>
<th>Deaths/million prescriptions (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic antidepressants and related drugs:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td>45</td>
<td>9</td>
<td>200.9 (92.0 to 381.6)</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>107</td>
<td>10</td>
<td>93.5 (44.8 to 171.8)</td>
</tr>
<tr>
<td>Dothiepin</td>
<td>26 210</td>
<td>1398</td>
<td>53.3 (50.5 to 56.1)</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>23 844</td>
<td>906</td>
<td>38.0 (35.5 to 40.5)</td>
</tr>
<tr>
<td>Imipramine</td>
<td>3 354</td>
<td>110</td>
<td>32.8 (27.0 to 39.5)</td>
</tr>
<tr>
<td>Doxepin</td>
<td>1 587</td>
<td>40</td>
<td>25.2 (18.0 to 34.3)</td>
</tr>
<tr>
<td>Trimipramine</td>
<td>2 370</td>
<td>39</td>
<td>16.5 (11.7 to 22.5)</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>4 315</td>
<td>54</td>
<td>12.5 (9.4 to 16.3)</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>1 269</td>
<td>7</td>
<td>5.5 (2.2 to 11.4)</td>
</tr>
<tr>
<td>Maprotiline</td>
<td>201</td>
<td>1</td>
<td>5.0 (0.1 to 27.7)</td>
</tr>
<tr>
<td>Trazodone</td>
<td>2 753</td>
<td>11</td>
<td>4.0 (2.0 to 7.1)</td>
</tr>
<tr>
<td>Mianserin</td>
<td>922</td>
<td>3</td>
<td>3.3 (0.7 to 9.5)</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>324</td>
<td>1</td>
<td>3.1 (0.1 to 17.2)</td>
</tr>
<tr>
<td>Lofepramine</td>
<td>7 189</td>
<td>9</td>
<td>1.3 (0.6 to 2.4)</td>
</tr>
<tr>
<td>Butriptyline</td>
<td>1</td>
<td>0</td>
<td>0 (0 to 3372)</td>
</tr>
<tr>
<td>Iprindole</td>
<td>3</td>
<td>0</td>
<td>0 (0 to 1218)</td>
</tr>
<tr>
<td>Viloxazine</td>
<td>10</td>
<td>0</td>
<td>0 (0 to 357.2)</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>94</td>
<td>0</td>
<td>0 (0 to 39.2)</td>
</tr>
<tr>
<td>Serotonergic drugs:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>2 570</td>
<td>34</td>
<td>13.2 (9.2 to 18.5)</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>660</td>
<td>2</td>
<td>3.0 (0.3 to 10.9)</td>
</tr>
<tr>
<td>Citalopram</td>
<td>2 603</td>
<td>5</td>
<td>1.9 (0.6 to 4.5)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>5 964</td>
<td>7</td>
<td>1.2 (0.5 to 2.4)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>19 926</td>
<td>18</td>
<td>0.9 (0.5 to 1.4)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>15 031</td>
<td>11</td>
<td>0.7 (0.4 to 1.3)</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>576</td>
<td>0</td>
<td>0 (0 to 6.4)</td>
</tr>
</tbody>
</table>
Correlates with FTI

- $>10^7$ prescriptions
- $10^6-10^7$ prescriptions
- $10^5-10^6$ prescriptions
- $<10^5$ prescriptions

$r^2 = 0.11$
$p < 0.0001$
FTIs ≠ toxicovigilance

Figure 4 (zopiclone)

Drug Safety 2004; 27 (2):135-41
FTIs – Measure impact of regulation (& toxicovigilance)

Figure 1

Drug Safety 2004; 27 (2):135-41
Figure 2

Barbiturates

Number of deaths, 10,000 Prescriptions & FTI

Prescriptions

* Number of deaths

Annual FTI

Year

82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99

0
100
200
300

SACTRC
Benzodiazepines

Figure 2

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of deaths, 100,000 Prescriptions &amp; FTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>82</td>
<td>300</td>
</tr>
<tr>
<td>83</td>
<td>250</td>
</tr>
<tr>
<td>84</td>
<td>200</td>
</tr>
<tr>
<td>85</td>
<td>150</td>
</tr>
<tr>
<td>86</td>
<td>100</td>
</tr>
<tr>
<td>87</td>
<td>50</td>
</tr>
<tr>
<td>88</td>
<td>0</td>
</tr>
<tr>
<td>89</td>
<td>0</td>
</tr>
<tr>
<td>90</td>
<td>0</td>
</tr>
<tr>
<td>91</td>
<td>0</td>
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<tr>
<td>92</td>
<td>0</td>
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<td>93</td>
<td>0</td>
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<td>94</td>
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<td>95</td>
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<td>96</td>
<td>0</td>
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<tr>
<td>97</td>
<td>0</td>
</tr>
<tr>
<td>98</td>
<td>0</td>
</tr>
<tr>
<td>99</td>
<td>0</td>
</tr>
</tbody>
</table>

- Prescriptions
- * Number of deaths
- Annual FTI
Total Benzodiazepine deaths
Temazepam deaths
Total temazepam prescriptions
Gelatin capsule prescriptions (92-99)

Year

Number of deaths & 100,000 prescriptions

IV abuse reported in Lancet
Advisory council warning
Voluntary bans
UK Ban announced
Gelatin capsules removed from market
*In December 2001, the Pharmaceutical Benefits Advisory Committee recommended that prescribing of temazepam capsules be restricted to people who have failed to respond to the tablets because of concerns about misuse by intravenous drug users.
Deaths from Co-proxamol (dextropropoxyphene/paracetamol) and other analgesic poisoning, and suicide by drug poisoning in the UK between 1998 and 2010

Overview

- Toxicovigilance
- Case reports
- Fatal toxicity indexes

**Relative clinical toxicity**
*(Clinical databases)*

- Overcoming current limitations?
  - Poisons centre network
  - Toxicovigilance laboratory
Table 2  Odds ratios for admission with self-poisoning (July 1989–June 1992, Hunter Valley origin) or primary cause of prescribed drug-related death corrected for prescription frequency

<table>
<thead>
<tr>
<th>Drug group</th>
<th>OR self-poisoning/prescription (95% CI)</th>
<th>OR for cause of prescription drug-related death/prescription (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td>10.6 (8.5–13.1)</td>
<td>11.6 (4.1–32.2)</td>
</tr>
<tr>
<td>Other barbiturates</td>
<td>43.2 (23.8–78.2)</td>
<td>523.7 (207–1322)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>6.6 (5.9–7.5)</td>
<td>0.3 (0.0–2.0)</td>
</tr>
<tr>
<td>Chlora hydrate</td>
<td>4.5 (2.0–10.0)</td>
<td>58.1 (18.1–187)</td>
</tr>
<tr>
<td>Colchicine</td>
<td>1.1 (0.2–8.0)</td>
<td>27.9 (3.8–202)</td>
</tr>
<tr>
<td>Dextropropoxyphene</td>
<td>1.3 (0.7–2.4)</td>
<td>20.8 (8.8–48.9)</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>7.5 (6.3–9.0)</td>
<td>3.9 (1.2–12.6)</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>5.4 (4.6–6.3)</td>
<td>13.3 (7.2–24.5)</td>
</tr>
</tbody>
</table>

OR, odds ratios; CI, confidence interval.

Table adapted with permission from Buckley et al.\textsuperscript{59}
Retrospective clinical data collection

✿ Adequate only for studies where
  – Cases can be found without selection bias
  – Outcomes are objective and routinely recorded
  – All deaths (in and out of hospital) are recorded

✿ Contrast the reliability of estimates of morbidity & mortality from a particular poisoning based on
  – Poison centre calls.
  – Hospital admissions.
  – Forensic data sets.
  – Prospective clinical and forensic database.
Needs to be Integrated into clinical practice

- Prospectively collect routine clinical data
- Preformatted admission charts
  - improve completeness of recording of clinical examination
  - collect more information than can be obtained retrospectively from case records

TOXICOLOGY ADMISSION

First medical contact (eg LMO/St Elsewhere's Hospital/Ambulance):

Method of transport (to Mater):

Exposure/overdose date and time:

Presentation date and time (to first contact):

Admission date and time (to Mater):

Type of admission:
- Deliberate self harm
- Recreational use
- Accidental poisoning
- Iatrogenic toxicity
- Other poisoning
- Envenomation

Substances ingested or exposed to (include alcohol and note other self harm eg. wrist laceration)

<table>
<thead>
<tr>
<th>Substance</th>
<th>No</th>
<th>Tablet strength</th>
<th>Whose medication?</th>
<th>Date prescribed</th>
<th>Dose/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patient's normal medication (whether taken in overdose or not)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/strength</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Weight (kg): 53
Height (cm): 172
Temp (°C): 36.4
Pulse Rate (bpm): 68
Blood Pressure (mm Hg): 118/69
SaO2: 95%

Skin Changes:
- Red or Flushed
- Cyanosis
- Jaundice
- Sweating

Bowel Sounds:
- Normal
- Absent
- Reduced
- Hyperactive

Respiration Category:
- Apnoea or Ventilated
- Cheyne-Stokes
- < 12 per minute
- 12 to 29 per minute (X)
- 30 to 39 per minute
- >= 40 per minute

Glasgow Coma Score (GCS): 15

Eye Opening:
1. None
2. To Pain
3. To Speech
4. Spontaneous

Best Verbal Response:
1. None
2. Incomprehensible
3. Inappropriate
4. Confused / Screaming
5. Oriented

Best Motor Response:
1. None
2. Extending (decerebrate)
3. Flexing (decorticate)
4. Flexing (withdrawal)
5. Localising pain
6. Obey commands

Refer to ICU if:
- GCS < 9
- Low BP
- Heart rate < 50 or > 120 bpm
- RR < 12, SaO2 < 90%
HATS - Keeping it simple (for 26 years)

- Clinical effects
- Time course of toxic effects
- Relative toxicity of related agents
- Diagnosis
- Prognosis
- Toxicokinetics
- Effects of Treatment (e.g. charcoal, dialysis)
Cardiotoxicity More Common in Thioridazine Overdose than with Other Neuroleptics

Nicholas A. Buckley, B.Med.*; Ian M. Whyte, M.B.B.S. (Hons)**; Andrew H. Dawson, M.B.B.S.**

*Clinical Pharmacology, University of Newcastle, Department of Clinical Toxicology, Mater Misericordiae Hospital; Newcastle, New South Wales, Australia
## Relative clinical toxicity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SE) or number (%) of patients</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dothiepin (n=67)</td>
<td>Other TCA (n=220)</td>
</tr>
<tr>
<td>Seizures</td>
<td>9 (13%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>4 (6%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>94 (2)</td>
<td>92 (1)</td>
</tr>
<tr>
<td>Glasgow coma score</td>
<td>11 (1)</td>
<td>12 (0)</td>
</tr>
<tr>
<td>Mean QRS (ms)</td>
<td>90 (3)</td>
<td>89 (1)</td>
</tr>
<tr>
<td>QRS ≥100 ms</td>
<td>17 (25%)</td>
<td>38 (17%)</td>
</tr>
<tr>
<td>Mean heart rate (bpm)</td>
<td>98 (2)</td>
<td>100 (1)</td>
</tr>
<tr>
<td>Mean QT (ms)</td>
<td>353 (5)</td>
<td>348 (3)</td>
</tr>
<tr>
<td>QTc (s²)</td>
<td>446 (3)</td>
<td>441 (3)</td>
</tr>
</tbody>
</table>

**Table 3: Outcome measures in dothiepin and other TCA groups**

*Lancet 1995;343:159-162*
Relative toxicity of venlafaxine and selective serotonin reuptake inhibitors in overdose compared to tricyclic antidepressants

I.M. WHYTE\textsuperscript{1,2}, A.H. DAWSON\textsuperscript{1,2} and N.A. BUCKLEY\textsuperscript{3}

From the \textsuperscript{1}School of Population Health Sciences, Faculty of Medicine and Health Sciences, University of Newcastle, Newcastle, NSW, \textsuperscript{2}Department of Clinical Toxicology & Pharmacology, Newcastle Mater Misericordiae Hospital, NSW, and \textsuperscript{3}The Canberra Hospital, Woden, ACT, Australia

Received 27 August 2002 and in revised form 5 February 2003
Not always keeping it simple

Population pharmacokinetics and pharmacodynamics of escitalopram in overdose and the effect of activated charcoal

Freek van Gorp,1,2 Stephen Duffull,3 L. Peter Hackett4 & Geoffrey K. Isbister2,5

1Department of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands, 2Department of Clinical Toxicology and Pharmacology, Calvary Mater Newcastle, Newcastle, Australia, 3School of Pharmacy, University of Otago, Dunedin, New Zealand, 4Clinical Pharmacology and Toxicology, PathWest Laboratory Medicine, Perth, WA, and 5Discipline of Clinical Pharmacology, University of Newcastle, NSW, Australia

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Keywords
escitalopram, overdose, pharmacodynamics, pharmacokinetics, QT interval

Received
10 April 2011

Accepted
30 July 2011

Accepted Article
26 August 2011

Published Online
Plots of the fraction of patients with an abnormal QT (QT >447 ms, RR = 762 ms) vs. time for doses ranging from 50 mg to 400 mg. A) shows the fraction of patients without SDAC and B) the fraction of patients with SDAC.
Relative toxicity

Annual HATS admissions vs Year

- 1987: 200
- 1992: 400
- 1997: 600
- 2002: 700
- 2007: 800
- 2012: 700

Drugs: Propranolol, Thioridazine, Pheniramine, Temazepam, Dextropropoxyphene, Barbiturates, Dothiepin, Escitalopram, Citalopram, Amisulpride, Alprazolam, Venlafaxine

SACTRC
HATS – other drugs

% of agents ingested

- Alcohol
- Paracetamol
- Salicylates
- Opioids
- NSAIDs
- Antihistamines
- Cardiac drugs
- Antibiotics

1987-91
1992-96
1997-01
2002-06
2007-11
Overview

- Toxicovigilance
- Case reports
- Fatal toxicity indexes
- Relative clinical toxicity (Clinical databases)

Overcoming current limitations?
- Timelines
- Response
Toxicovigilance implies that the most urgent and important problems are a priority.

<table>
<thead>
<tr>
<th>Urgent and Important</th>
<th>Urgent but not Important</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important but not Urgent</td>
<td>Neither Urgent nor Important</td>
</tr>
</tbody>
</table>
The main limitation of current toxicovigilance
Toxicovigilance implies that the most urgent and important problems are a priority.

- **Urgent and Important**: Prescription opioid abuse
- **Urgent but not Important**: Antipsychotic metabolic effects
- **Important but not Urgent**: Synthetic cannabis
- **Neither Urgent nor Important**: Energy drinks
Is “toxicovigilance” simply the gathering of human evidence?

Table 1 Clinical data required for ‘evidence-based’ medicine in toxicology according to possible primary data sources

<table>
<thead>
<tr>
<th></th>
<th>Case report/ small series</th>
<th>Large selected series</th>
<th>Collection of all cases within a defined area and time</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiologist/ public health physician/ regulatory authorities</td>
<td>Burden of disease</td>
<td>—</td>
<td>Incidence/prevalence</td>
<td>As for unselected series only if these data are also collected and presented for the whole group eligible to enter the trial</td>
</tr>
<tr>
<td></td>
<td>People affected</td>
<td>—</td>
<td>Morbidity/mortality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Relative contribution of the different drugs</td>
<td>—</td>
<td>Age/gender and other risk factors</td>
<td></td>
</tr>
<tr>
<td>Clinician</td>
<td>Diagnosis/ symptomatology Investigations</td>
<td>Range of effects</td>
<td>Relative frequency</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range of effects</td>
<td>Differences in toxicity</td>
<td></td>
</tr>
<tr>
<td>Management</td>
<td>Hypothesis generation</td>
<td>Hypothesis generation</td>
<td>Frequency of symptoms/signs</td>
<td>Proof of efficacy of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sensitivity/specificity (if not affected by selection bias)</td>
<td></td>
</tr>
<tr>
<td>Forensic pathologists, coroners, medical examiners</td>
<td>Cause of death</td>
<td>Range of concentrations of drugs in plasma/tissues in therapeutic use and in poisoning</td>
<td>Mean, median, CI and range of values</td>
<td></td>
</tr>
</tbody>
</table>

RCT, randomized clinical trial; CI, confidence interval.
Table adapted with permission from Buckley and Smith.¹⁸
Engaging regulators

- Toxicovigilance implies there is a response
- Events leading to regulatory change often seem to relate to the sizzle more than the steak
  - Timing
  - Spin on the facts
  - Human story
  - Pictures
  - Local
- Case reports >>> data mining
  - (David & Goliath)
Poisons centres & Data mining

uestra or hope??
Three examples:

- Arsenic poisoning with 16 cases of food related illness within one hour called to one PIC
  - One lab did the important detection work
  - No regulatory intervention
- Detection of a test CBR incident
- Detection of food poisoning during blackout.
Childhood Injuries From Artificial Nail Primer Cosmetic Products

Alan Woolf, MD, MPH; Judith Shaw, RN, MPH

**Background:** Methacrylic acid–containing primers used in artificial nail cosmetic products are typically not contained in child-resistant packaging, although they are sold to the general public.

**Objective:** To analyze the type and severity of childhood poisoning injuries involving methacrylic acid–containing artificial nail primers.

**Design:** Secondary analysis of 2 national, population-based injury data sets.

**Setting:** The 1991 through 1993 National Electronic Injury Surveillance System data on emergency department visits compiled by the Consumer Product Safety Commission and the 1993 through 1995 Toxic Exposure Surveillance System data on calls to poison control centers compiled by the American Association of Poison Control Centers.

**Subjects:** Children younger than 6 years with injuries associated with exposures to nail primers.

**Results:** In the National Electronic Injury Surveillance System, there were 769 exposures to nail preparations, 32 (4.2%) of which involved nail primers. Twenty-eight (87.5%) of 32 nail primer exposures involved children younger than 6 years. Of the severe nail primer injuries, 80% involved preschoolers; most of the injuries were dermal burns. In the Toxic Exposure Surveillance System data set, there were 759 methacrylic acid–containing nail product exposures, of which 567 (74.7%) occurred in children younger than 6 years. Of exposures in preschool children, 56 (9.9%) resulted in moderate severity injuries and 3 (0.5%) in "major" injuries; there were no deaths.

**Conclusions:** Artificial nail primers containing methacrylic acid represent a corrosive hazard to young children and have been associated with severe injuries. New product labeling and packaging regulations and public education measures that recognize this hazard are recommended.

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**Conclusions:** Artificial nail primers containing methacrylic acid–containing primers used in artificial nail cosmetic products are typically not contained in child-resistant packaging, although they are sold to the general public.

New product labeling and packaging regulations and public education measures that recognize this hazard are recommended.
Scientific limitations

- PIC data rarely (if ever) leads to regulatory interventions
- Chance association vs. causation
  - Prospective (confounding by indication)
  - Retrospective (+ case finding, data collection bias)
  - No out-of-hospital outcomes (ascertainment bias)
  - Call centres (+++ case finding, follow up bias)
Planning to do it better

Problem Identified

Planning

Intervention

Measure impact

Toxico-vigilance

Identify problems / issues for investigation

reflect on and evaluate action

carry out research

formulate action plan
Prospective PIC studies

(need defined hypotheses, objective outcomes)

Amisulpride Overdose Is Frequently Associated With QT Prolongation and Torsades de Pointes

Geoffrey K. Isbister, BSc, MBBS, FACEM, MD,*† Corrine R. Balit, BPharm, MBBS,‡
Dawson Macleod, BPharm,§ and Stephen B. Duffull, BPharm, PhD//

Abstract: This study aimed to describe the effects of the antipsychotic amisulpride in overdose, including the frequency of QT prolongation and torsades de pointes. Cases of amisulpride overdose (>1 g) were recruited from 2 state poison centers and a tertiary toxicology unit over 5 years. A 1-page clinical research form was used to collect clinical information. Copies of all electrocardiograms were obtained. Electrocardiograms is listed in the product information, although details of its occurrence were unavailable (Sanofi Aventis Australia, personal communication, 2005).

There are numerous reports of different drugs causing an abnormal QT or QTc in overdose,6 and patients with an acutely abnormal QT require continuous telemetry because of concerns about development of TdP. However, despite these concerns.
Toxicovigilance limitations - conclusions

- Data mining has yet to strike pay dirt
- Case reports hampered by inadequate laboratory support (for the undead)
- Clinical databases including death data are rare
- Fatal toxicity data are derived far too late to merit the word ‘vigilance’
- The response to identified issues is haphazard & slow
- Current efforts driven by what data we collect – (not what we need)
How could toxicovigilance improve in Australia

- Coordinated approach - collect data most likely to identify urgent and important problems early
  - Poisons centres/Clinical toxicology treatment centres
  - National coronial database
  - Developing world imports
    - manufacturing/ agricultural/ medicinal

- Much better lab support
- Data mining
  - Better signal to noise
    - specificity of exposure
- Notifiable diseases?
It’s going to work.

Sucrosa®
Placebo

It’s a pill.

Laboratory studies have shown Sucrosa (placebo) to be occasionally effective in the treatment of pain and discomfort associated with chronic rhinitis, allergies, hives, sinusitis, arthritis conditions, ankylosing spondylitis, fibromyalgia, gout, lupus, osteoarthritis, psoriatic arthritis, rheumatic arthritis, rheumatoid arthritis, asthma, acute and chronic pain, low back pain, inflammatory bowel disease (IBD), abdominal pain, ulcerative colitis, constipation, diarrhea, dyspepsia (indigestion), intestinal gas, heartburn, hemorrhoids, irritable bowel syndrome (IBS), lactose intolerance, constipation, motion sickness, ankle pain, tendinitis, bursitis, heel spurs, knee pain, lower back pain, muscle cramps, tinnitus, vertigo, asthma, erectile dysfunction, migraine headaches, attention deficit disorder (ADD), bedwetting, lactose intolerance, rheumatoid arthritis, sleep disturbance, rosacea, scleroderma, shingles, insomnia, jet lag, narcolepsy, sleep apnea, somnolent, urinary incontinence, urinary tract infections, premenstrual syndrome, and yeast infections.

Side effects associated with the use of a placebo include alterations in heartbeat; increased blood pressure and cold extremities; muscle weakness, stiffness, and spasm; muscle and bone pain; nervousness; decreased mental sharpness; tremor; headache; abnormal sensation; vertigo; sleep disturbance; mood and personality changes; alterations in speech and movement; memory impairment; confusion and dream abnormality; stomach upset; diarrhea; dry mouth; constipation; gas; thirst; acid reflux; difficulty swallowing; changes in appetite; burping and inability of the tongue to move; flushing; hot flashes; sweating; itching; rash; acne; skin reaction to sunlight; difficult or rapid breathing; dryness or discomfort of the throat or nose; nose bleed; yawning and sinus disorder; cold-like symptoms; cough; hiccups; visual disturbances; ringing in the ears; ear pain; eye discomfort; swelling or tearing; alterations in hearing and smelling; visual intolerance to light and bad taste; allergic reactions including swelling of face, lips, tongue, and/or throat, which may cause difficulty in breathing and/or swallowing; wheezing; hives; rash; severe sloughing of the skin; chills; heat sensitivity; swelling; bloating; hangover effect; fever; fainting; dizziness on standing up; warm/cold sensations; dehydration; and changes in urination and menstruation.