Medication errors and pharmacovigilance

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Birmingham
Errors are part of life

An error occurs when an action is intended but not performed

A medication error is a failure in the treatment process that leads to, or has the potential to lead to, harm to the patient

Reason J. Human Error 1990

EMA: WC500196979 2014

Lancet 2000; 355: 947-8

Drug Safety 2006; 29:1011-22
Scope for error in medication

Pharma
- Develop
- Make

Both
- Provide information-SmPC

Prescriber
- Consider & discuss information
- Prescribe
- Dispense
- Giver
- Monitor
- Administer

Regulator
- Ensure safety, quality, efficacy

NICE &c
- Provide guidance
Error in development

TGN–1412, an anti-CD28 superagonist

Six of eight subjects became very ill

Primate studies misinterpreted
Few *in vitro* human studies
Prediction of dose range from animal studies unreliable
No ‘proper interval’
Preparation for possible ADR(cytokine storm) inadequate
Error in development

BIA-102474-101 Fatty acid amide hydrolase inhibitor

48 Single dose studies – no ADRs with active
32 Multiple dose studies – no ADR with active
Cohort no 5 dose 50 mg/day on Day 5 of 10
5 subjects alright; one admitted to hospital
Day 6 → further doses → all five admitted
Error in manufacture

1937 sulfanilamide in diethylene glycol
107 die as a result
1938 US Food Drug & Cosmetic Act

• Fatal renal failure caused by diethylene glycol in paracetamol elixir: The Bangladesh epidemic
• Fatalities Associated with Ingestion of Diethylene Glycol-Contaminated Glycerin Used to Manufacture Acetaminophen Syrup -- Haiti, November 1995-June 1996

MMWR 1996 Aug 2; 45: 649-50
FAMILIES SUE OVER CANCER DRUG ERROR

HUMAN error led to 13 children with leukaemia being given an overdose of chemo-therapy, the chief executive of Birmingham Children's Hospital said yesterday.

- Labelled ‘correctly’ as vincristine
- Diluted wrongly, so concentration $\times 2$
Error in packaging

Report of three children with eye injuries from superglue

‘reported frequently since 1982 when superglue was repackaged into ophthalmic style dropper bottles’

Desai Arch Dis Child 2005; 90:1193
Error in information

Pro-Epanutin™ 75mg/ml Concentrate for Solution for Infusion

The recommended initial maintenance dose of Pro-Epanutin of 4 to 5 mg PE/kg/day …

FDA warning: “The reference incorrectly states that fosphenytoin is supplied as a solution with a concentration of 75 mg PE/mL.”

PE = phenytoin sodium equivalents

Gahart BL. Intravenous Medications, 15th edn, Mosby 1999
Errors in prescribing (on paper)

- Prescribed Digoxin 250 mg IV
- Given Digoxin 2.5 mg IV
- Result = Death (probably)
## Errors in (electronic) prescribing

**Pick list**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine sulfate concentrated oral solution</td>
<td>= 20 mg/ml</td>
</tr>
<tr>
<td>Morphine sulfate oral solution 10mg/5ml</td>
<td>= 2 mg/ml</td>
</tr>
<tr>
<td>Morphine sulfate oral solution 10mg/5ml</td>
<td></td>
</tr>
<tr>
<td>Oramorph concentrated oral solution 20mg/ml</td>
<td></td>
</tr>
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<td>Oramorph oral solution 10mg/5ml</td>
<td></td>
</tr>
</tbody>
</table>
Errors in dispensing

Baby died because they were prescribed 20 times the level of chloroform required
Errors in dispensing

Emily Jerry, 2 years old

- Last cycle of chemotherapy
- Etoposide made up in saline

Technician used saline 23.4% not 0.9%

Pharmacist failed to notice

Emily died
Pharmacist jailed
‘Involuntary manslaughter’
Errors in administration

...does not prevent the need for surgery nor reduce mortality
Discussion

The failure to demonstrate a beneficial effect on the healing of gastric ulcers with continuous intragastric milk drip is disappointing.
Errors in administration

INADVERTENT INTRAVENOUS INFUSION OF MILK

J. R. WALLACE  R. W. PAYNE  A. J. MACK
Victoria Infirmary, Glasgow G42 9TY

A patient with an exacerbation of a duodenal ulcer received 100 ml. of pasteurised cow’s milk by intravenous infusion

- Anaphylaxis
- DIC
- Fat embolism

Lancet 1972; i: 1264–5
Errors all round

Two haematology patients with febrile neutropenia die within hours

BMJ 2007; 335: 467
Amphotericin dose mg/kg

- Fungizone®: Initial dose 0.1 × 20 = 2
- AmBisome®: Maximum dose 5
- Abelcet®: Maximum dose 5

× 20
Amphotericin

- Doctor trained to use approved names
- Doctor unused to standard preparation
- Prescription for amphotericin ambiguous
- Nurses unused to liposomal formulation
- Regulator failed to warn beforehand
Pharmacovigilance and safety

- Before the event – e.g. History; Escoffier; users;
- After the event – e.g. gathering data and acting on them
Scope for errors in medication

• Complexity encourages error

• Surtout faites simple!
**West Midlands Centre for ADRs**

**Colchicicine (BNF)**

**Adult** 500 micrograms 2–4 times a day until symptoms relieved, maximum 6 mg per course, do not repeat course within 3 days

---

**Patient has gout**

- **Course within 3 days?**
  - No → **Are symptoms relieved?**
  - Yes → **Four tablets today?**
  - No → **Total dose = 6 mg?**
  - Yes → **Give**
  - Yes → **Give**

---

**Do not give further colchicine**

---

22 Patient has gout

Course within 3 days? No Yes

Are symptoms relieved? Yes No

Four tablets today? Yes No

Total dose = 6 mg? Yes No

Give

---

West Midlands Centre for ADRs
OC - contraindication

‘history of breast cancer

• but can be used after 5 years
• if no evidence of disease
• and non-hormonal methods unacceptable.’
Better $\beta$-test

• Test in routine use
• Ask the users
• (Thimbleby and IV smart pumps)
Failure modes & effect analysis

Characterize the elements or steps in the process
Identify modes of failure
For each process element, score
- severity of undetected failure
- likelihood of occurrence for each failure
- likelihood that failures will escape detection
→ Calculate a risk priority for each process step

Adachi Am J Health-Syst Pharm 2005; 62:917-20
After marketing

- Pharma:
  - Develop
  - Make

- Both:
  - Provide information - SmPC

- Prescriber:
  - Consider & discuss information
  - Prescribe
    - Dispenser
      - Dispense
    - Giver
      - Administer

- Monitor

- Regulator:
  - Ensure safety, quality, efficacy
  - NICE &c
    - Provide guidance

- Error reports
- Case reports
- News
Conclusions

• Errors occur at every stage
• Good design could reduce errors
• Past experience could reduce errors before marketing
• Pharmacovigilance could detect errors post-marketing
• There is more to do
What needs to be proved
Pharmacovigilance

Science and activities relating to:
Detection
Assessment
Understanding
Prevention
Of adverse effects or any other medicine-related problems
Scope for errors in medication

- Complexity encourages error

- Surtout faites simple!

Auguste Escoffier
Colchicicine (BNF)

- Adult
  - 500 micrograms 2–4 times a day until symptoms relieved, maximum 6 mg per course, do not repeat course within 3 days.

**Patient has gout**

**Course within 3 days?**

- **No**
  - Are symptoms relieved?
    - **No**
      - Four tablets today?
        - **No**
          - Total dose = 6 mg?
            - **No**
              - Give
        - **Yes**
          - Ye
      - **Yes**
        - Ye
    - **Yes**
      - Ye
  - **Yes**
    - Ye

**Do not give further colchicine**
Did the error cause the harm?

Very hard to judge in individual cases

Naranjo’s algorithm

DoTS – consider

dose, time-course, susceptibility of patient

‘Between the eyes’ – everyone can see the causal link
Did the error cause the harm?

My expert opinion:
Experts underestimate the danger of hindsight bias

Three medico-legal problems

Was there harm?

Harm

Was there error?

Therapeutic act

Error

Did the error cause the harm?

Error

Harm
To prove negligence, have to prove:

- Therapeutic act
- Negligence
- Harm

But often:

- No negligence
- Negligence
- Harm
The (criminal) ‘but for’ test:

But for the error, there would have been no harm

Therapeutic act → Negligence → Harm

Therapeutic act → No negligence → No harm
The (civil) 'but for' test:

But for the error, there would (probably) have been no harm
IV paracetamol: 10 mg or 10 mL?

Drug safety advice

Intravenous paracetamol (Perfalgan ▼): risk of accidental overdose, especially in infants and neonates

Keywords: intravenous paracetamol, Perfalgan (▼)

Vigilance is advised when prescribing and administering intravenous paracetamol 10 mg/mL solution for infusion (Perfalgan ▼) to ensure that the correct dose is given. For all patients, dose requirement is based on weight as outlined below and in the product information. For infants and children who weigh less than 33 kg, the 50 mL vial should be used for administration.

MHRA
2010
Picking and choosing

→ Hypotension, bradycardia
Three medical problems

Was there error?
Was there harm?
Did the error cause the harm?
Case 4: Was there error?

Two haematology patients with febrile neutropenia die within hours

Agency warns about dosing error for amphotericin

Two patients in an oncology ward at Birmingham Heartlands Hospital in July after being treated with the wrong formulation of injectable amphotericin—a drug to treat fungal infections.

The National Patient Safety Agency (NPSA) has issued a warning over the use of the drug, but without disclosing where the two deaths referred to in its announcement had taken place. When questioned, the NPSA and the hospital confirmed that the deaths had taken place within hours of each other.

BMJ 2007; 335: 467
Case 4: Was there error?

- Prescribed by doctor
  Amphotericin IVI 5 mg/kg
- Given by nurses
  Amphotericin IVI 5 mg/kg
  → two patients die
Case 2: Was there error?

**TGN–1412, an anti-CD28 superagonist**

Six subjects became very ill

- Primate studies misinterpreted
- Few *in vitro* human studies
- Prediction of dose range from animal studies unreliable
- No ‘proper interval’
- Preparation for possible adverse events (cytokine storm) inadequate
Deferasirox

Soluble tablets
Initially 10–30 mg/kg
once daily

Film coated tablets
14 mg/kg
Case 5: Was there error?

Frail 81-year-old man
Awaiting percutaneous gastrostomy – nil by mouth
‘Do not attempt cardiopulmonary resuscitation’
Hypertensive, treated with ramipril, bisoprolol, doxazocin
Case 6: Systematic failures

36-year-old care worker

• Holiday in Spain
• Infected insect bite
• Allergic to penicillin
• Recorded in notes, on allergy band
• Consultant in a hurry
Case 6: Systematic failures

- Junior doctor absent from W/R
- Consultant: ‘Prescribe Magnapen’
- Nurse at inquest:
  ‘I knew she was allergic to penicillin, but not that Magnapen was penicillin’
- Consultant at inquest:
  ‘I simply advised the junior doctor to prescribe’
Case 6: Systematic failures

Teresa Innes, who was left brain-damaged and in a coma from which she never recovered after being prescribed penicillin.
Benzydamine powder is intended for the preparation of solutions for external gynaecological use only and its incorrect oral intake may cause systemic adverse reactions.
Fungizone®
• Test dose 1 mg, to be given over 20–30 minutes, then 250 micrograms/kg daily, gradually increased over 2–4 days, increased if tolerated to 1 mg/kg daily
• AmBisome®
• Test dose 1 mg, to be given over 10 minutes, then 3 mg/kg once daily; maximum 5 mg/kg per day
Wrong units

77-year-old
- Severe depressive episode
- Psychotic features
- Delusions that she was being poisoned

- Fast atrial fibrillation → oral digoxin
**Wrong units**

<table>
<thead>
<tr>
<th>Date</th>
<th>Drug (approved name)</th>
<th>Dose</th>
<th>Time</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/10/10</td>
<td>Digoxin</td>
<td>250 mcg</td>
<td>0400</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>500 mcg</td>
<td>1140</td>
<td>IV</td>
</tr>
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Errors in (electronic) prescribing

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A hospital has apologised for a ‘terrible, one-off accident’ which resulted in the death of a pensioner.

Wrong calculation

Prescribed

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Given
Negligence

1. A owed a duty of care to B
2. A breeched that duty of care
3. B suffered harm as a result
4. The harm was a reasonably foreseeable consequence of what A did
Scope for error in medication

**Pharma**
- Develop
- Make

**Regulator**
- Ensure safety, quality, efficacy
Error in packaging

Shouldn’t the company and the regulator have seen this coming?
1. A owed a duty of care to B
2. A breeched that duty of care (was negligent)
3. B suffered harm as a result
4. The harm was reasonably foreseeable
A HOSPITAL has apologised for a ‘terrible, one-off accident’ which resulted in the death of a pensioner.
Distracted doctor 'killed two patients suffering just ulcers with TEN TIMES normal dose of morphine while he surfed the internet'

- Both patients, aged 78 and 86, died of morphine poisoning