The need for Pharmacovigilance

Shanthi Pal
Quality Assurance and Safety of Medicines
What is Pharmacovigilance?

WHO definition:

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

This applies throughout the life cycle of a medicine equally to the pre-approval stage as to the post-approval.
Why do we need pharmacovigilance?

Will PV prevent these?
No medicinal product is entirely or absolutely safe for all people, in all places, at all times. We must always live with some measure of uncertainty. PV can characterise that risk.
Why do we need pharmacovigilance?

Ten reasons why....
Why do we need pharmacovigilance?

Reason 1:
- Insufficient evidence of safety from clinical trials
Drug Development

Clinical development of medicines

**Phase I**
- 20 – 50 healthy volunteers to gather preliminary data
- Animal experiments for acute toxicity, organ damage, dose dependence, metabolism, kinetics, carcinogenicity, mutagenicity/teratogenicity

**Phase II**
- 150 – 350 subjects with disease - to determine safety and dosage recommendations

**Phase III**
- 250 – 4000 more varied patient groups – to determine short-term safety and efficacy
- Post-approval studies to determine specific safety issues

**Phase IV**
- Spontaneous Reporting
- Post-approval studies to determine specific safety issues

Preclinical Animal Experiments  
Phase I  
Phase II  
Phase III  
Phase IV  
Spontaneous Reporting  
Registration
Rule of 3

- There is 95% chance of observing one occurrence of an event in a population 3 times the size of the event’s frequency
  - e.g. if the incidence is 1 / 10 000
  - 30 000 patients to find one case
'other' limitations of phase 1 - 3 clinical trials

- narrow population: age and sex specific
- narrow indications: only the specific disease studied
- short duration: often no longer than a few weeks
Reason 2

Medicines are supposed to save lives

*Dying from a disease is sometimes unavoidable; dying from a medicine is unacceptable.* Lepakhin V. Geneva 2005
UK:

It has been suggested that ADRs may cause 5700 deaths per year in UK.

*Pirmohamed et al, 2004*

US:

ADRs were 4th-6th commonest cause of death in the US in 1994

*Lazarou et al, 1998*
Reason 3

- To **KEEP** products on the market
### Examples of product recalls due to toxicity

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Year</th>
<th>Examples of serious and unexpected adverse events leading to withdrawal of medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>1965</td>
<td>Phocomelia</td>
</tr>
<tr>
<td>Practolol</td>
<td>1975</td>
<td>Sclerosing peritonitis</td>
</tr>
<tr>
<td>Clioquinol</td>
<td>1970</td>
<td>Subacute nephropathy</td>
</tr>
<tr>
<td>Benoxaprofen</td>
<td>1982</td>
<td>Nephrotoxicity, cholestatic jaundice</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>1997</td>
<td>Torsade de pointes</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>2004</td>
<td>Cardiovascular effects</td>
</tr>
<tr>
<td>Veralipride</td>
<td>2007</td>
<td>Anxiety, depression, movement disorders</td>
</tr>
</tbody>
</table>
But…

Is product recall the aim of PV?
No because...

- No drug is inherently safe
  - unless it has no effect at all!

- Each patient is unique

- Each treatment situation is unique
  - What is the right drug for me might be a bad choice for you

- Understanding this will help make the right choice for each patient

if patients do well, so will the drugs (but not necessarily the other way around!)
Reason 4

To protect patients from unnecessary harm

Many ADRs are preventable
Adverse drug reactions in hospital in-patients: a pilot study

E. C. Davies*†, MPharm MRPharmS, C. F. Green† BSc Hons PgDipClinPharm PhD MRPharmS, D. R. Mottram‡ BPharm PhD, FRPharmS and M. Pirmohamed*§ MBChB PhD FRCP

- 125 Patients
- 24 Patients experienced ADRs (19%)

(59%) were avoidable
Burden of ADRs
Mumbai, India

- 6.9 % of hospital admissions
- 0.85% fatality
- 60% avoidable

## Preventable problems

### TABLE 2.1

Studies of Preventable Drug-Related Hospital Admissions

<table>
<thead>
<tr>
<th>Author, Year, Country (reference no.)</th>
<th>Sample Size</th>
<th>DRAs as % of Admissions</th>
<th>PDRAs as % of Admissions</th>
<th>Preventability Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bero et al., 1991, U.S. (4)</td>
<td>224</td>
<td>21.1</td>
<td>15.2</td>
<td>76</td>
</tr>
<tr>
<td>Bigby et al., 1987, U.S. (7)</td>
<td>686</td>
<td>10.6</td>
<td>6.3</td>
<td>59</td>
</tr>
<tr>
<td>Courtman and Stallings, 1995, Canada (8)</td>
<td>150</td>
<td>14.0</td>
<td>12.0</td>
<td>86</td>
</tr>
<tr>
<td>Cunningham et al., 1997, U.K. (9)</td>
<td>1011</td>
<td>5.3</td>
<td>4.3</td>
<td>80</td>
</tr>
<tr>
<td>Darchy et al., 1999, France (10)</td>
<td>623</td>
<td>6.6</td>
<td>4.8</td>
<td>73</td>
</tr>
<tr>
<td>Dartnell et al., 1996, Australia (11)</td>
<td>965</td>
<td>5.7</td>
<td>3.7</td>
<td>66</td>
</tr>
<tr>
<td>Hallas et al., 1992, Denmark (12)</td>
<td>1999</td>
<td>8.0</td>
<td>3.8</td>
<td>47</td>
</tr>
<tr>
<td>Lakshmanan et al., 1986, U.S. (13)</td>
<td>834</td>
<td>4.2</td>
<td>2.3</td>
<td>54</td>
</tr>
<tr>
<td>Lindley et al., 1992, U.K. (14)</td>
<td>416</td>
<td>6.3</td>
<td>3.1</td>
<td>50</td>
</tr>
<tr>
<td>Ng, et al., 1999, Australia (16)</td>
<td>172</td>
<td>18.0</td>
<td>5.8</td>
<td>32</td>
</tr>
<tr>
<td>Nikolaus et al., 1992, Germany (17)</td>
<td>87</td>
<td>25.3</td>
<td>12.6</td>
<td>50</td>
</tr>
<tr>
<td>Raschetti et al., 1997, Italy (18)</td>
<td>1833</td>
<td>2.5</td>
<td>1.4</td>
<td>56</td>
</tr>
<tr>
<td>Trunet et al., 1980, France (19)</td>
<td>325</td>
<td>7.1</td>
<td>4.3</td>
<td>61</td>
</tr>
<tr>
<td>Trunet et al., 1986, France (20)</td>
<td>1651</td>
<td>5.9</td>
<td>2.6</td>
<td>44</td>
</tr>
</tbody>
</table>

**Median** 623, **Minimum** 87, **Maximum** 1999

Reason 5

To reduce healthcare expenses

ADRs are a huge burden!!
6.5% of admissions are due to ADRs

Seven 800-bed hospitals are occupied by ADR patients

Cost £446 million per annum
Cost of ADRs in the US?

- Cost of drug related morbidity and mortality exceeded $177.4 billion in 2000 (Ernst FR & Grizzle AJ, 2001: J American Pharm. Assoc)

- ADR related cost to the country exceeds the cost of the medications themselves
More recent data from EU as a whole

Cost due to ADRs in EU: € 79 billions/year

Cost due to ADRs
Mumbai, India

- Additional cost to hospital INR 6197/patient (US$150)

Reason 6
Because any medicine can be implicated

<table>
<thead>
<tr>
<th>England</th>
<th>Mumbai</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID</td>
<td>Anti-TB</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Antiepileptics</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Antimalarialis</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Anticoagulants</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Oral antidiabetics</td>
</tr>
</tbody>
</table>
Reason 7

Promoting rational use of medicines and adherence
Prescription

Dr A. Who

31 December 2000

Re: Mr Joseph Bloggs

1) abacavir + lamivudine + zidovudine 1 BD
2) atenolol 100 mg/d
3) acetylsalicylic acid 150mg/d
4) cerivastatin 10 mg/d
5) gemfibrozil 200 mg/d
6) metformin 500 mg/d
7) fluoxetine 50 mg/d
8) Sildenafil
Main reasons of discontinuation of first HAART regimen within 1st year: ICONA

Monforte et al. AIDS 1999
Reason 8

Ensuring public confidence

*If something can go wrong, it will – Murphy's law*
MALARIA is a dangerous disease. It accounts for about 1.44 per cent of all deaths in Africa.

The experiences of malaria on its victims include but not limited to loss of appetite, headache, fever, general body pains, among others.

When malaria strikes, it sends its victims running helter-skelter, seeking refuge in traditional, as well as orthodox, medicine. People have resorted to all sorts of drugs and herbs to cure themselves of this ailment.

In Ghana, we have, at one time or the other, administered Camoquine, Nevaquine, Artesunate, Chloroquine, or Halofan to malaria patients.

Each of these malaria drugs has its own known side effects. The thrust of this article is, however, to discuss the debilitating side effects of Artesunate-Amodiaquine — a new malaria drug recently introduced on the Ghanaian market.

I am not a medical doctor and I do not pretend to be one. However, as a patient, I wish to highlight my personal experience with Artesunate-Amodiaquine after a brief encounter with malaria.

I had malaria on Friday, October 20, 2006. I was given a packet of tablets containing two sets of drugs called Artesunate-Amodiaquine. Each set had three tablets.

I was asked to take one of each set at regular intervals for three consecutive days, namely, Friday, Saturday and Sunday. I dutifully took the drugs as prescribed.

The side effects were, however, quite devastating. I experienced dizzy-ness, nausea, general body pains and a low blood pressure recorded as 80/40.

I immediately became an emergency case, leading to my detention in a private clinic for three hours. I was resuscitated through intensive care and three drips of glucose.

After that traumatic experience, I went back to the hospital to do a malaria test. I tested positive and was given Halofan. So the questions that arise are:

- What is the therapeutic efficacy of Artesunate-Amodiaquine?
- Is it a curing or a killing drug?
- What is the safety profile of the drug?
- Should such a drug be administered in Ghana in the light of the danger it poses?
- Should the drug enjoy the wide media coverage it currently enjoys?
- Should it be withdrawn?

From my personal experience, I think the efficacy of Artesunate-Amodiaquine is in serious doubt. How else can a drug meant to cure us of malaria incapacitate its user and leave the malaria parasites to enjoy a field day? In other words, the drug seems to brutalise its user and allow the malaria parasites more room to operate and break down the resistance of the patient.

A thorough scientific analysis ought to be carried out on the drug to determine its true therapeutic and curative efficacy. We do not have time to wait for lives to be lost before we start thinking about what to do.

After narrating my horrifying experience to some colleagues and friends, I was informed that many more patients had suffered similar side effects as I did.

It may not be surprising that some of us were used as the guinea pigs. We are even told that camoquine is a banned drug in Europe and the Americas.

If that is true, why should it be used in Ghana? Is our country the dumping ground for banned drugs and substances?

Given the effect it has on innocent patients, it is surprising that Artesunate-Amodiaquine is still in circulation in Ghana. It ought to have been withdrawn by now.

A wide media campaign was recently launched to popularise the use of the drug. For those of us who have suffered severe side effects from the use of the drug, we firmly believe that once bitten, twice shy.

By John Nketia
Reason 9

Ethical thing to do

To know of something that is harmful to another person who does not know, and not telling, is unethical.
Not reporting a serious unknown reaction is unethical

valid for everyone

- patient
- health professional
- manufacturer
- authorities
Consequence

ALLEGATION:
Known about SSRI prescribing at unsafe doses for a decade

Guardian Weekly
March 18-24 2004
Reason 10

It can unveil lapses in BEST PRACTICES

- Unexpected lack of effect
  - counterfeiting
  - resistance
  - interaction

- Quality problems

- Dependence and abuse

- Poisoning

- Medication errors
Pharmacovigilance
Major Aims

- early detection of unknown safety problems
- detection of increases in frequency
- identification of risk factors
- quantifying risks
- communicating information
- preventing patients from being affected unnecessarily

Rational and Safe use of Medicines
Pharmacovigilance is Essential