

## Pharmacovigilance and Reporting Adverse Drug Reactions

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### PHARMACOVIGILANCE AND REPORTING ADVERSE DRUG REACTIONS

Drug therapy is an essential part of health care and has become a universally accepted form of medical treatment, both by health professionals and society at large. It is not an exaggeration to say that almost every human being has had an experience with drug therapy, even newborn infants are now exposed to immunisations on the day they are born. What does society want from drug therapy? Walley (1995) summarised the needs of the public as the '3 E', efficacy, effectiveness and efficiency.

- Efficacy: the drug works (fulfils its intended purpose) under optimal conditions, and is safe and tolerable
- Effectiveness: the drug works under the conditions of everyday use
- Efficiency: be defined as for every dollar spent, the greatest possible benefit is gained.

Pharmacovigilance deals with the first 2 Es of drug therapy; efficacy and

effectiveness. Any substance capable of producing therapeutic effect also produces unwanted or adverse effects. It is therefore important to identify any adverse drug effect to eliminate or minimise morbidity and mortality due to drug use. ADRs harmfully affect patient's quality of life, increase cost of patient care and cause patients to lose confidence in their doctors and their treatment.

The year 1961, after the thalidomide disaster, that pharmacovigilance really took a foothold with huge international effort to address the issue of drug safety. An Australian obstetrician, William McBride reported an increase in foetal malformations with unique characteristics, later known as phocomelia, in the babies of mothers prescribed the drug thalidomide (Routledge 1998). Dissemination of information was relatively slow and by the time thalidomide was withdrawn, thousands of babies were born with phocomelia and other disabling congenital malformations. There was a huge public outcry and governments

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worldwide especially within Europe and the United States recognised there was a need to regulate and monitor the safety of drug use. This led to the Sixteenth World Health Assembly (1963) which adopted a resolution for the rapid dissemination of ADRs information, and prompted the creation of the WHO Pilot Research Project for International Drug Monitoring in 1968 (World Health Organization 2002a). This pilot research became the basis for pharmacovigilance systems worldwide and later resulted in a WHO consultation meeting in 1971 which advocated the establishment of national centres for drug monitoring and provided the first guidelines for national centres (World Health Organization 2002a).

According to the World Health Organisation (WHO) pharmacovigilance is defined as the science and activities (observational or post-approval scientific data gathering activities) relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems with the goals of identifying and preventing these problems to the extent possible (World Health Organization 2002a). The most important task of pharmacovigilance is to identify 'signals' of drug safety problems as early as possible. A signal is defined by the WHO as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously" (World Health Organization 2002b). A 'safety signal' refers to a concern about an excess of adverse events

compared to what would be expected to be associated with a product's use (Food and Drug Administration 2005). According to earlier reports, the ultimate goal of pharmacovigilance is to foster the rational and safe use of medicines, the assessment and communication of the risks and benefits of drugs on the market and educating and informing of patients (Uppsala Monitoring Centre 2000).

A new medicine must pass three hurdles before its approval by the national drug regulatory authority. Sufficient evidence is required to show the new drug to be (World Health Organization 2004):

- Of good quality
- Effective
- Safe for the purpose or purposes for which it is proposed

Whereas the first two criteria must be met before approval, the issue of safety is less certain. Safety is not absolute and can only be judged in relation to efficacy and limits of acceptable safety. Frequently when a new drug is marketed, many of its known adverse effects including those describe within the summary of product characteristics (SPC) and in textbooks are adverse effects establish during the third phase of drug trial (out of 4). This knowledge is often incomplete especially in regards to frequency, mechanism and risk factors. Tests in animals are insufficient to predict human safety. There is also a possibility that rare yet serious adverse events (such as those occurring with a frequency of one in two thousands) will not be detected in

the pre-registration development of the drug. Prior to drug approval for market, it will have to be exposed to a number of patients to detect its efficacy and toxicity. However, due to the limitation of number of patients exposed (ranging from as few as 500 to 5000), the condition of use differ from 'real world' clinical practice, the limited duration of clinical trials and increasing pressure on drug regulators from the pharmaceutical industry to shorten the review time for new medicines, detection of these less frequent adverse events is almost nil (Table 1) (Strom 2006). A fatal ADR occurring in 1 in 2000 patients treated with a new drug will only be recognized after 6000 patients have been treated and observed, and this is only likely provided that the background incidence of such a reaction is zero or a causal association with the drug is clear (Strom 2006). Even if detected, the event will be incompletely described and understood because of too few events. In addition, it may also be difficult to use clinical trials to ascertain the safety profile associated with chronic exposure to any product, exposure in populations with co-morbid conditions or taking multiple medications. More information is also frequently needed for drug use in specific population groups such as children, pregnant women and the elderly due to homogenous sample populations in clinical trials. Drug-drug interactions are also frequently not assess with much detail during the drug development process.

It was the thalidomide disaster (a teratogen) which started the era of pharmacovigilance; with much irony however pharmacovigilance involving

Table 1: Practicality of detecting adverse drug reactions in clinical trials or post-marketing

Expected incidence of adverse drug reactions	Required number of patients to detect one event with 95 percent power
1 in 100	300
1 in 200	600
1 in 1000	3000
1 in 2000	6000
1 in 10000	30000

pregnant women has not developed significantly since the disaster occurred. Drug trials and research involving pregnant women have been almost non-existent resulting in a gap in knowledge regarding which drugs are suitable for use during pregnancy. ADRs affect everyone and children are not spared. It is reported that 9% of children experience ADRs while in hospital and that approximately 0.8% of children suffers a fatal outcome with ADRs. Both figures are likely to be an underestimate, as it is well recognised that ADRs are significantly under reported (Clarkson & Choonara 2002) Over 50% of medicines used in children may not have been studied in this age group (MHRA 2013)

### DEFINITIONS AND CLASSIFICATION OF ADRS

There are various definitions for ADRs and ADEs, some of which are widely used while others have been proposed. The conventional and widely accepted definitions are proposed by the Uppsala monitoring centre (UMC) and the world health organisation (WHO) (Uppsala Monitoring Centre 2000; Uppsala Monitoring Centre). In defining ADR/E,

various other related terms are defined as follows:

- A **drug** or **medicine** is a pharmaceutical product, used in or on the human body for the prevention diagnosis or treatment of disease, or for the modification of physiological function.
- An **adverse (drug) reaction** is a response to a medicine which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function. (Normal dose clause distinguishes adverse reactions from poisoning and this clause was later refined by Meyboom et al. (2000), to caution on patients experiencing an adverse reaction at normal dose but may indeed be a case of high/toxic dose because of impaired renal/hepatic excretion or other reasons. It is common for the term **adverse effect** to be used as synonyms for adverse reaction. Adverse effect is seen from the point of view of the drug whereas an adverse reaction from the point of view of the patient (Edwards & Aronson 2000). Another commonly used definition for an ADR was put forward by Edwards and Aronson (2000), who define an ADR as “an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen or withdrawal of the product”. The Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom has a broader definition of an ADR “as an unwanted or harmful reaction experienced following the administration of a drug or combination of drugs, which is suspected to be related to the drug” (British Medical Association 2006). Unlike the WHO definition, the MHRA definition does not exclude overdose or drug misuse.
- An **unexpected adverse reaction** is an adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorisation, or expected from characteristics of the drugs.
- A **side effect** is any unintended effect of a pharmaceutical product occurring at doses normally used in man, which is related to the pharmacological properties of the drug.
- A **toxic effect** is an adverse effect of a drug which occurs as an exaggeration of the desired therapeutic effect and which is not common at normal doses (Edwards & Aronson 2000). It is always dose-related.
- An **adverse event** or **experience** is defined as any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with the treatment.
- **Serious** (not synonymous with ‘severe’ which is used to describe the intensity of a specific outcome) adverse events/reactions can be

defined as those that:

- are life threatening or fatal
- cause or prolong hospital admission
- cause persistent incapacity or disability
- concern misuse or dependence
- **Efficacy** is the ability of a drug to produce the intended effect as determined by scientific methods, for example in pre-clinical research conditions.

### RECOGNISING ADRS

Without the ability to recognise ADRs, it becomes meaningless to define ADRs. Recognising ADRs is not clear-cut as ADRs may act through the same physiological and pathological pathways as the disease being treated. A patient's drug history should include details regarding illicit drugs, herbal and homeopathic medicines, detailing any suspected drug-drug interaction and cross-reactivity. Concurrent viral infections may also increase the risk of ADRs; infectious mononucleosis increases the risk of rash in patients given amoxicillin by a factor of 58 (Pirmohamed 2005). Genetic factors may also be related to an ADR; patients with Glucose-6-phosphate dehydrogenase (G6PD) deficiency will suffer from red cell haemolysis when prescribed primaquine.

The following steps published by the WHO are usually recommended to be undertaken to identify an ADR (World Health Organization 2002b):

- Ensure the medicine ordered is actually taken by the patient at the dose advised
- Verify the onset of the suspected ADR was after the drug was taken
- Determine the time interval between beginning of drug treatment and onset of adverse event
- Evaluate the suspected ADR after discontinuing the drug(s) or reducing the dose. If appropriate, restart the drug treatment to monitor recurrence of adverse event.
- Analyse alternative causes
- Use up-to-date literature, national pharmacovigilance centre and personal/colleague experience to verify previous reports/experience on the ADR.

### CAUSALITY ASSESSMENT

Once an ADR/E is recognised, the next step is to determine the cause of the ADR/E. Most case reports in pharmacovigilance are for 'suspected' ADR/Es. ADR/Es are rarely specific for a drug, and often without a confirmatory diagnostic test except for a re-challenge which is rarely ethically justified. Few ADR/Es are certain. It is often quoted "Report it if you are unsure". The WHO as well Malaysia's national pharmacovigilance centre advises to report an ADR/E even if you are unsure of the cause of the ADR/E or you believe it to be unlikely that an ADR/E has occurred. When in doubt, report it.

### IMPORTANCE AND RELEVANCE OF IDENTIFYING AND DETECTING ADRS/ADES

ADRs affect a significant number of patients. A two year prospective

study in the UK involving 19 general practitioners and 872 patients by Martys (1979) reported that up to 41% of patients had some type of adverse drug effect with 90% of the adverse effect occurring by the fourth day of prescription (Martys 1979). A prospective cross sectional study of a representative nationwide (33 hospitals) sample of medical wards by Pouyanne et al. (1998) reported that 3.19% (100 out of 3137) of patients were admitted to hospital because of an adverse drug reaction. The patients tended to be older and were more likely to be female. Four (0.12%) patients died as a direct result of the adverse effect. The authors however do caution that a larger proportion of adverse effects probably occur in the community but do not give rise to hospital admission. A meta-analysis commonly cited as a reference is by Lazarou et al. (1998) which analysed 39 pharmacovigilance studies. The meta-analysis reported the incidence of serious ADRs to be 2.1%, incidence of fatal ADRs to be 0.19% and overall incidence of ADRs to be 10.9% for in hospital patients. The incidence for patients admitted to hospital due to serious ADRs is 4.7% and with fatal ADRs is 0.13%. The overall ADR incidence was reported to be 15.1% of hospital patients. Lazarou et al. (1998) then estimated 106 000 deaths were caused by ADRs in the United States (1994) which would indicate fatal ADRs to be the fourth to sixth leading cause of death.

A meta-analysis of 68 studies involving a total of 123 794 patients by Beijer and Blaey (2002) reported that 4.9% (CI 0.1%) of hospital admissions are related to ADRs. Twelve studies

provided data on unnecessary hospital admissions, of which 407 out of 1410 (28.9%) were regarded as preventable. Beijer and Blaey (2002) also reported that in people aged over 65 years, the admission rate due to a suspected ADR was higher (16%) compared to the younger individuals (4%). A cost estimate for Netherlands was reported in which the authors estimated that preventable ADR related admissions cost the Netherland health care system was £110 to £256 million, annually (Beijer & Blaey 2002). A summary of 13 studies by Goettler et al. (1997) reported that ADRs are responsible for a mean length of stay in hospital of 9.6 days with a median of 8.7 days. They also noted that annual direct cost of hospital admissions due to ADRs (1997) for Germany was approximately 1050 Million DM (525 million Euro) and more importantly 30.7% of admissions due to ADRs were preventable, providing a potential savings of 350 million DM (175 million Euro) (Goettler et al. 1997).

A two year observational study by Buajordet et al. (2001) examined the cause of death for 732 patients out of a total of 13 992 admissions. Buajordet reported 18.2% (133 out of 732) of deaths were classified as fatal adverse drug events (FADE) with 64 (48%) of the deaths caused directly by one or more drugs. Half of the cases (66/133) were judged to be related to various degrees of inappropriate administration or use of drug(s), therefore potentially avoidable (Pirmohamed et al. 2004).

More recent data were provided by Pirmohamed et al. (2004) with his prospective study involving 18 820 patients admitted to two hospitals in

Merseyside over a six month period. Pirmohamed et al. (2004) reported that ADRs caused 1225 admissions (6.5%, 95% CI of 6.2% to 6.9%) with 95% classified as type A ADRs. More importantly, Pirmohamed et al. (2004) reported 72% of the ADRs were avoidable. The proportion of women admitted was significantly higher in the ADR group (59% vs 52%) compared to the non-ADR group. 2.3% of patients died as a direct result of the index ADR (0.15% of all patients admitted) suggesting that ADRs are responsible for the death of approximately 5700 patients annually. Patients admitted with an ADR had a median stay of eight days resulting in the projected annual cost of ADR related admissions to the NHS of £466 million. This cost estimate does not include ADRs suffered by patients while being hospitalised and ADRs in primary care that did not result in hospital admissions. A pilot study in 2006 by Davies et al. (2006) assessed ADRs which occurred during hospitalisation rather than the cause of admission. They reported that 19.2% (24 out of 125 patients) of patients suffered one or more ADRs while hospitalised with a median length of stay which was significantly longer than patients admitted for other reasons (14.5 days vs. 8 days) (Davies et al. 2006). With the rising cost of health care (bed occupancy cost and treatment cost), it would be safe to assume that the current cost of ADRs to the health services in the UK should have exceeded £500 million pounds, possibly approaching £2 billion in 2014.

ADRs affect all patient populations, although information regarding special

populations such as children and pregnant women are limited. In a 10 year retrospective study by Le et al. (2006) at the Miller Children's Hospital, US, the overall incidence of ADRs per hospital admission was 1.6% with an annual incidence of 0.4 -2.3%. However, this study omitted patients with medication errors and patients suffering ADRs out of hospital. Impicciatore et al. (2001) conducted a systematic review and meta-analysis to determine the incidence of ADRs in the paediatric population. The review included 17 studies. Impicciatore reported a higher overall incidence of ADRs among hospitalised children of 9.53% (95% CI: 6.81 to 12.26) when compared with Le et al. (2006) with severe reactions accounting for 12.29% of the total. The overall rate of paediatric admissions due to ADRs was 2.09% (95% CI: 1.02 to 3.77) with 39.3% of the ADRs being severe reactions. The overall incidence of ADRs was 1.46% (95% CI: 0.70 to 3.03) for outpatient children.

## PHARMACOVIGILANCE IN MALAYSIA

It is clear by now that little information has been quoted from Malaysia. Information from Malaysia is scanty and pharmacovigilance researches are frequently underpowered to be referenced. Funding for pharmacovigilance type research is almost non-existent, although clearly lacking and urgently needed. It should be noted that Malaysia has been a member of the WHO Programme for International Drug Monitoring since the year 1990. However, Malaysia's

contribution towards the programme could be classified as moderate at best. Although there are currently 118 member countries contributing to the programme, it is widely acknowledged that most contributions to the programme originate from a few countries, mainly the United States, Europe and Japan.

Pharmacovigilance in Malaysia is under the responsibility of the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) which was established under Drug Control Authority (DCA). MADRAC provides DCA with important information pertaining to local and international drug safety issues, as well as advises DCA on risk management and risk communication following effective assessment of the benefit-risk profile of drugs. The National Centre for Adverse Drug Reaction Monitoring acts as the secretariat to MADRAC (MADRAC 2012). The main form of ADR reporting system in Malaysia is a spontaneous reporting system, frequently known as the 'blue card' system as the card used to report ADR is blue in colour. As the name suggests, this form of reporting system is voluntary and is frequently plagued by low reporting rates. A systematic review by Hazell and Shakir (2006) reported the median under-reporting rate from 37 studies across 12 countries was 94% with an under-reporting rate of 80% for more serious ADRs. In the UK, the number of ADR reports has remained stable at 25 000 per year for the past 10 years (MHRA 2014). In Malaysia, the number of reports has average at less than 6000 for the past 10 years (Bulletin MADRAC

2014). Reporting of ADR to MADRAC has seen an increase for the past 5 years, doubling from 5850 reports in 2009 to 11473 reports in 2013. This increase is partly due to reinforcement of ADR reporting for immunization, which contributes approximately a fifth of all ADR reports (Bulletin MADRAC 2014). However, further analysis reveals a less positive scenario. Pharmacist contributes the majority of reports (54.7%), followed by ministry of health doctors (13.6%) and product registration holders (10.8%). General practitioners (GPs) and private specialists contributed a meagre 1% of reports. These figures are for the year 2013 (BM 2014) although the trend does not deviate far from this in previous years. Unlike the UK, reports from GPs form the backbone of ADR reporting with total reporting from doctors contributing to almost 50% (MHRA 2014). As doctors, certain important information that would help in causality assessment as well as severity assessment is readily available when compared to other health professionals. MADRAC has now shifted its focus on quality reports instead of quantity. The WHO Uppsala Monitoring Centre measures individual case safety report quality using a score system between 0 (poorly documented case) to 1 (well documented). Over the past five years, reports from Malaysia have consistently obtained an average completeness score of around 0.45 (Bulletin MADRAC 2014). It is however not prudent to advise that only doctors should report an ADR, however the importance and the advantages of doctors reporting ADR encountered must be stressed repeatedly.



Spontaneous reporting is the principal pharmacovigilance system in use worldwide with proven effectiveness and a good track record resulting in the avoidance of many potential disasters and the identification of new or previously unknown drug related adverse effects. Its main advantages include wide population coverage, relatively low cost and resource utilisation (given the huge number of population covered and the continuous monitoring of all drugs), and a well established methodology (British Medical Association 2006; Meyboom et al. 1999) However, spontaneous reporting systems depend on voluntary reporting of health care professionals, hence the reporting rate or under-reporting rate becomes the limiting factor determining the success and usefulness of such an approach to pharmacovigilance. In Malaysia, low reporting rates causes signals to be not generated and even if generated, are often late. We instead rely on warnings and precautionary statements from the US and Europe, which is a weakness that needs to be looked into further and not ignored. Drugs marketed in Malaysia, our population, our environment and most importantly our prescribers are inherently different from the US and Europe. Relying on signals from countries with many differences is a weakness which unfortunately is difficult to overcome. The warnings may not affect Malaysia as the drug may not even be marketed here or as an Asian population, we may respond differently. Much more worrying however is the opposite. ADR/Es occurring commonly here but is not detected because no

signals is being generated from the US or Europe.

## CONCLUSION

There is a common misconception especially among the public that all drugs approved by the authorities have all their side-effects or possible adverse reactions known and that the role of the authorities is to monitor any drug on the market for unexpected adverse reactions and to withdraw drugs from the market. In fact, the number of drug withdrawals on the grounds of quality, efficacy, and safety has remained relatively stable since the 70s with only 24 withdrawals out of 583 new active substances (new chemical, biological or pharmaceutical substances for human consumption) approved between 1972 and 1994 with a 10 year survival of all new active substances at approximately 88%, a low attrition rate when compared with other consumer products (Jeffrey et al. 1998). This brings forward an important task for pharmacovigilance, the dissemination of information and educating society regarding drug safety and pharmacovigilance. The message that an approved drug does not mean 100% safety and the identification of unknown adverse reactions after marketing approval is necessary must be presented with tact to avoid mass panic and greater misunderstanding. The recognition of adverse reactions, including serious adverse reactions does not automatically justify the withdrawal of a drug from the market. A balanced assessment between benefit and harm must be made and this assessment

should be presented to the public and more importantly to health practitioners, to reduce harm and maximise the benefits. This will however remain a challenge in the foreseeable future for pharmacovigilance and national health authorities in particular, because at the core of this objective coming to realization is improving ADR/E reporting rates.

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