Editorial: Medication safety - why is Phase 4 adverse drug reaction monitoring important?

Traditionally, the focus of medicine registration has been on pre marketing studies. Formal post marketing Phase 4 studies evaluating a medicine’s efficacy have been extremely limited. Over time, ongoing studies have provided some guidance, but often not for many years, if at all. This limitation also applies to medicines added to the Pharmaceutical Benefits Scheme; however, recently it has emerged that the Pharmaceutical Benefits Advisory Committee will finally be paying more attention to this issue.

On the other hand, post marketing Phase 4 monitoring of medication safety has always received attention, for obvious reasons. Unfortunately, some of this monitoring has not been as systematic as desirable. This is due to factors such as the dependence on voluntary reporting, and because many adverse drug reactions (ADRs) are not identified as being medication related. Another challenge is the difficulty in accurately determining the frequency with which a particular medicine is used in relation to the incidence of an ADR to that medicine. The introduction of e-prescribing throughout the hospital will assist with this later aspect.

Nevertheless, despite methodological limitations, ADR monitoring and reporting has provided a great deal of extremely valuable information on the safety of medicines.

Why report?
A common misconception over the years has been the assumption that extensive clinical trials, prior to marketing, have enabled all the medicine’s adverse effects to be detected. There are a number of reasons why this is not so, some of which are:

- ADRs with a low incidence may not be detected in clinical trials because the number of patients treated is not sufficient to detect the problem. For instance, an ADR that occurs with an incidence of 1 in 1000 patients treated (0.1%), would require the treatment of 30,000 patients in order to have a 95% chance of detecting the ADR; if the incidence was 1 in 10,000 (0.01%), we would need 30,000 patients to be treated.
- Some ADRs have a long lead time before they are fully expressed.
- Clinical trials exclude many high risk patients which, of course, must be done on ethical and safety grounds. However, post marketing, these patients with risk factors may well encounter the medicine. Factors such as medication interactions, contraindications, incorrect dosage and inappropriate use of medicines, can all come into play.
- There is extensive medication safety monitoring required in clinical trials to enable the early detection of ADRs prior to them becoming a more serious problem. Unfortunately, the need for such intensive monitoring is not always emphasised to the prescriber once the medicine is approved for marketing.

Therefore, there is a need for ongoing vigilance in Phase 4 of the life of a medicine. The benefits of such monitoring include:

- Characterisation of ADRs to facilitate their early detection and the initiation of corrective action.
- Compilation of a database to estimate the relative incidence of a particular ADR.
- Identification of risk factors for a particular ADR to a medicine which can then be utilised in education strategies to raise awareness to the risk.

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• Accurate recording of ADRs, especially immune-mediated reactions, and this information then documented in the patient’s health record to ensure a patient is not re-exposed to that medicine.

What happens at Monash Health?
At Monash Health, the Pharmacy Department has been managing an extensive ADR monitoring and review process for over 20 years. A great deal of emphasis has been placed on educating, training and promoting the need to report ADRs and attempting to make the reporting process easier. This approach has been relatively successful in obtaining a large number of prospective, voluntary ADR reports.

A positive secondary outcome of Casemix funding has been the need for accurate coding of patient episodes of care, using the International Classification of Diseases 10th Revision Australian Modification (ICD-10-AM). This coding system includes Y codes that relate to medicines causing adverse effects. The ADR Pharmacist reviews a monthly report of all patient episodes of care which have been assigned a Y code. The health records of selected patients are then reviewed and any ADRs identified are documented.

All ADRs reported are documented on the ‘Report of Suspected Adverse Drug Reaction (ADR01)’ form in the patient’s health record. Importantly, patient ADR details are also entered into the e-prescribing system and also appear in the patient’s scanned medical record; a critically important role to ensure a patient is not re-exposed to that particular medicine. To further assist in this matter, Adverse Drug Reaction (ADR) Alert cards are issued to the patient and information is also passed on to the patient’s community medical practitioner.

The ADR reports obtained are stored in our local ADR database and a deidentified copy of the report form is also sent to the Advisory Committee on the Safety of Medicines (ACSOM) who, in turn, sends them for inclusion in the World Health Organisation (WHO) database.

The ADR Review Subcommittee of the Therapeutics Committee meets regularly and examines the ADRs recorded at Monash Health, particularly ones that may be potentially avoidable. The information gained from these reviews is used to develop educational strategies including:

- Medication Safety Alerts (posters)
- Therapeutic updates (emails)
- Articles in The Encapsulator
- Lectures and tutorials.

In times past, the reporting of ADRs has often been thought of as being an unproductive or bureaucratic activity. It is hoped that this brief overview of our systems will enable a greater understanding of the process and its importance. Making the system work is in everyone’s interest.

Ian Larmour - Editor

Allergies and adverse drug reactions training
The Monash Health Medication Safety Committee has developed an online Allergies and Adverse Drug Reactions (ADR) Training course available on Monash Health Learning.

The training covers: definitions of the terms allergy, anaphylaxis and ADR; how to perform an accurate patient allergy and ADR history; documentation of allergy and ADRs in the patient’s electronic and paper health record; safe practices to prevent re-exposure of an allergen to patients with a previous known allergy or ADR and penicillin allergy, including recognising penicillins and other beta-lactam antibiotics.

The training involves an interactive learning package followed by the successful completion of a quiz. All clinical staff involved in prescribing, administering and dispensing medicines are required to complete the training every three years.

Monash Health staff can access the training via Monash Health Learning and search for ADR.

Ticagrelor induced shortness of breath - therapeutic update

When is ticagrelor used?
Ticagrelor is an antiplatelet medicine that reversibly binds to the P2Y12 adenosine diphosphate receptor to inhibit platelet aggregation. It is used for the treatment of acute coronary syndrome in combination with aspirin. Ticagrelor, in combination with aspirin, can be considered as an alternative to clopidogrel and aspirin or prasugrel and aspirin in people with an acute coronary syndrome.

Precautions: ticagrelor may cause dyspnoea
Dyspnoea is more common among people taking ticagrelor than clopidogrel. In Phase 2 studies, ticagrelor was associated with a dose-dependent incidence of dyspnoea of 10.20% compared to 0-6.4% with clopidogrel. Dyspnoea is usually mild (recognised as being present but easily tolerated) or moderate (causing discomfort sufficient enough to interfere with normal activities). The symptoms of dyspnoea often begin within seven days of starting treatment with ticagrelor. The PLATO study showed that most episodes of dyspnoea lasted for more than 20 days and may persist for the duration of ticagrelor therapy. Older people, people with asthma, chronic obstructive pulmonary disease or heart failure and people with a history of dyspnoea appear to be more likely to experience dyspnoea. Ticagrelor should be used with caution in these patients.

Why does ticagrelor induce shortness of breath?
The mechanism of ticagrelor induced dyspnoea is not yet fully understood. Ticagrelor induced
dyspnoea has not been associated with acidosis or any adverse changes in patient pulmonary or cardiac function. It is hypothesised that the sensation of dyspnoea in ticagrelor treated patients is triggered by adenosine because ticagrelor inhibits its clearance, thereby increasing its concentration in the circulation.

Information for patients
Patients should be advised that ticagrelor may cause shortness of breath and they should see a doctor if they experience prolonged or worsening shortness of breath or if it prevents them from carrying out their usual activities. If the decision is made to cease ticagrelor, immediate replacement with clopidogrel or prasugrel is required.

Monash Health Pharmacy Department research:
Treatment of Acanthamoeba Granulomatous Amoebic Encephalitis in an immunocompromised patient: a case report

Objective
To describe the medication management of a rare infection, Acanthamoeba Granulomatous Amoebic Encephalitis (GAE).

Clinical features
A 66 year old man presented with generalised tonic-clonic seizures, fever, one month of confusion and seven months of worsening vision. He had multiple co-morbidities including Cryptogenic Multifocal Ulcerous Stenosing Enteritis (CMUSE) treated with prednisolone, hemicolectomy and ileostomy secondary to CMUSE, and chronic renal impairment (admission CrCl = 34 mL/min). A brain computed-tomography showed a left occipital lobe lesion.

Interventions, case progress and outcomes
Phenytoin and carbamazepine were started for seizures on Day 1. On Day 5, blood cultures were positive for gram positive coci (Staphylococcus epidermidis) and vancomycin 1g IV bd started. Benzylpenicillin 2.4g IV 4 hourly, meropenem 1g IV tds and aciclovir 600mg IV tds were started on Day 13 for acute meningoencephalitis. On Day 14, cerebrospinal fluid results were positive for Cryptococcus antigen and liposomal amphotericin 6mg/kg IV daily and flucytosine 25mg/kg PO qid started, vancomycin continued and acyclovir, meropenem and benzylpenicillin ceased.

Amiodarone 200mg PO tds was started for atrial fibrillation secondary to sepsis on Day 15 (changed to metoprolol on Day 27). On Day 19, piperacillin with tazobactam and ciprofloxacin were started. On Day 20, piperacillin with tazobactam was ceased and meropenem started due to greater central nervous system penetration. Ciprofloxacin was ceased on Day 25 secondary to QT prolongation.

On Day 35, the brain biopsy result indicated an 88% match for Acanthamoeba and Acanthamoeba GAE was diagnosed. The United States based Centers for Disease Control (CDC) and Prevention was contacted for management advice and recommended early initiation of a multidrug antimicrobial regimen based on previous case reports. Fluconazole 400mg IV daily, cotrimoxazole 160/800mg IV tds and azithromycin 500mg IV daily were added to liposomal amphotericin, with miltefosine to commence when available.

Miltefosine, a Therapeutic Goods Administration (TGA) unapproved medicine, was sourced from the United States via the TGA Special Access Scheme and started on Day 40 at 50mg PO tds, ceasing on Day 53 secondary to gastrointestinal adverse effects. By Day 76, the patient clinically improved and liposomal amphotericin was ceased. The patient started rehabilitation on Day 83. However, on Day 87 the patient developed further complications; palliative care was started on Day 104 and the patient died on Day 106.

The complexity of medication management in this patient enabled significant scope for pharmacist input. These included: dose review (with or without modification) for renal impairment (vancomycin, benzylpenicillin, meropenem, aciclovir, flucytosine, piperacillin with tazobactam, ciprofloxacin, fluconazole and cotrimoxazole) and ongoing renal function monitoring; vancomycin and flucytosine therapeutic drug management; managing multiple potential medicine interactions (including ciprofloxacin and amiodarone, fluconazole and liposomal amphotericin); monitoring for potential adverse drug reactions; sourcing miltefosine and providing medicines information to clinicians on the use of these medicines.

Conclusion
With limited case studies published, there is little guidance on the management of Acanthamoeba GAE. Management included a complex medication regimen requiring significant pharmacist input. It is hoped this case report contributes to the evidence available to guide clinicians on the medication management of Acanthamoeba GAE and the role of the pharmacist within the clinical team.

Tiffany Wan, Rula Azzam

Adverse drug reaction: Rabeprazole-induced tinnitus

Tinnitus is a common medical symptom that can be debilitating and sometimes life-changing. It has been associated with a wide range of medicines. Some of the medicines which have been implicated include aminoglycosides, diuretics, non-steroidal anti-inflammatory agents and antineoplastic agents. Rabeprazole-induced tinnitus has not been previously reported.

A 39 year old man experienced tinnitus after taking two doses of oral rabeprazole 20mg. His medical history included gastro-oesophageal reflux disorder (GORD). He denied
ever using alcohol, herbal and over-the-counter medicines. Physical examination including the neurological system was within normal limits. Complete blood count and biochemical tests were also within normal ranges. After ceasing rabeprazole, the patient was consulted by an otorhinolaryngologist. No abnormalities were detected. Forty-eight hours after cessation of rabeprazole, tinnitus resolved spontaneously. Due to the recurrence of GORD symptoms, rabeprazole was recommenced. Three days later, the tinnitus returned. Once again rabeprazole was ceased and the tinnitus was resolved in the following days.


Updated recommendations for pertussis vaccination in pregnancy and early childhood

Pertussis (whooping cough) is a respiratory infection caused by *Bordetella pertussis* with an incubation period of 7 to 20 days. In unvaccinated persons, *B. pertussis* is highly infectious, spreading by aerosols to 90% of susceptible household contacts. Natural infection does not provide long-term protection and repeat infection can occur.

It has been estimated that *B. pertussis* accounts for up to 7% of cough illnesses per year in adults. Pertussis can be associated with significant morbidity in adults, with cough persisting for up to 3 months. Death is rare in people aged 10-70 years. However, the case-fatality rate in unvaccinated infants <6 months of age is estimated to be 0.8%. Infants are at greatest risk until they can have at least two doses of the vaccine (minimum 4 months old) as the mother’s antibodies do not provide reliable protection.

Pertussis vaccine is available in Australia only in combination with diphtheria, tetanus and other antigens. The acronym DTPa, signifies child formulations of diphtheria, tetanus and acellular pertussis-containing vaccines (Infanrix Hexa®, Infanrix-IPV®). The acronym dTpa is used for formulations that contain substantially lesser amounts of diphtheria toxoid and pertussis antigens than child (DTPa-containing) formulations; dTpa vaccines (Boostrix®, Adacel®) are usually used in adults and children over 10 years.

It is very relevant at this time to note that, in line with recommendations in the United Kingdom and the United States, the 2015 draft updated chapter on Pertussis in *The Australian Immunisation Handbook, 10th Edition* includes recommendations that all pregnant women receive a booster dose of dTpa vaccine during the third trimester of each pregnancy, ideally between the 28th to 32nd week of gestation, regardless of when they have previously received the vaccine. As stated in the draft updated chapter, “vaccine-induced pertussis antibodies wane over time and the protective antibody level required in newborn infants is unknown. It is therefore possible that if a mother is not revaccinated during a subsequent pregnancy (even if closely spaced), her newborn will not be adequately protected”.

The draft updated chapter also addresses the issue of “blunting”, which suggests maternal pertussis antibodies can inhibit active pertussis-specific antibody production in infants after administration of DTPa vaccine to infants of mothers vaccinated with dTpa during pregnancy. The draft updated chapter recommends that an additional booster dose of a pertussis-containing vaccine at 18 months of age be given to children born to mothers who received the vaccine during pregnancy. This additional booster vaccine was also recommended by the Pharmaceutical Benefits Advisory Committee at its November 2014 Meeting.

Another recommendation in the 2015 draft updated chapter is that adult household contacts and carers (e.g. fathers, grandparents) of infants less than 6 months of age should ideally receive a dTpa vaccine at least 2 weeks before beginning close contact with the infant.

Finally, it is expected that both the recommendation of vaccination against pertussis in the third trimester of pregnancy and the additional booster dose of a pertussis-containing vaccine, given to the child at 18 months of age - when incorporated into *The Australian Immunisation Handbook, 10th Edition* - will form part of an updated and publicly-funded “Immunise Australia Program” at the earliest possible opportunity so as to minimise the risk of young infants acquiring pertussis infection. The Victorian Department of Health and Human Services has committed to providing the dTpa vaccine free to pregnant women in their third trimester or new parents as soon as possible after the birth as soon as a supply of vaccine has been secured, which may take up to six months. In the interim, the vaccine is available through private prescription.