AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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☆ Aripiprazole and Neuroleptic Malignant Syndrome
☆ Varicella vaccine experience in Australia
☆ Drugs of Current Interest

Please report all suspected reactions to these Drugs of Current Interest

Atomoxetine (Strattera)
Ezetimibe/Simvastatin (Vytorin)
Fenofibrate (Lipidil)
Iron sucrose (Venofer)
Lumiracoxib (Prexige)
Moxonidine (Physiotens)
Pregabalin (Lyrica)
Rosuvastatin (Crestor / Viacor)
Teriparatide (Fortéo)
1. Aripiprazole and Neuroleptic Malignant Syndrome

ADRAC has previously noted that the two oldest of the atypical antipsychotics, clozapine and olanzapine, can cause neuroleptic malignant syndrome (NMS).\(^1,2\) In fact, it appears from reports to ADRAC that all of the atypical antipsychotics available in Australia, as well as the traditional antipsychotics, can cause this problem. The number of reports of NMS (and as a percentage of the total number of reports received for the medicine) is shown below:

- Clozapine: 85 reports (2.3%)
- Olanzapine: 49 reports (4.1%)
- Quetiapine: 16 reports (5.2%)
- Risperidone: 45 reports (5.7%)
- Amisulpride: 15 reports (6.7%)
- Aripiprazole: 15 reports (10.3%)

Spontaneous reporting has many biases that make comparisons difficult. Although it appears that, of the atypical antipsychotics, NMS occurs most frequently with aripiprazole, this trend is not shown in reports to the worldwide database maintained by the World Health Organisation (WHO). Aripiprazole (Abilify) has been available in Australia since 2003 and since that time, 145 reports have been received. As indicated above, 15 describe NMS.

Clinical features of NMS include fever, confusion, disorientation or other cognitive function changes, muscle rigidity, profuse sweating, and autonomic instability. Increased creatine kinase (CK) is often noted. NMS can be life-threatening and rapid recognition and treatment are important. In the 15 ADRAC reports with aripiprazole, signs and symptoms were not described in 3 cases and in another 3 cases only an increase in CK was reported. Common features of the other 9 reports were increased CK (7 cases), fever (6), significant cognitive impairment (5), sweating (4) and tachycardia (4). As with NMS related to clozapine, significant rigidity does not seem to occur in many cases of NMS related to aripiprazole.\(^1\) Time to onset was not often stated but when it was, it was usually after a few days to a few weeks after starting aripiprazole. In a number of cases, aripiprazole had been added to pre-existing clozapine or olanzapine therapy.

Prescribers are reminded that NMS can occur in association with all atypical antipsychotics, including aripiprazole.

References:

2. Varicella vaccine experience in Australia

Since November 2005 varicella vaccine has been recommended on the Australian Standard Vaccination Schedule and funded for all children at 18 months of age and for children aged 10-13 years who have not received varicella vaccine or who have not had chicken pox. Varicella is usually a mild disease in healthy children but it can be severe in adults and can cause serious and even fatal illness in people of any age. In a 12 month period (1998–1999), there were 1,991 hospitalisations in Australia for varicella, with 8 in-hospital deaths.\(^1\) The majority of deaths occurred in previously healthy individuals.\(^2\)

Following the introduction of widespread vaccination in 2002 in the USA, hospitalisations due to varicella declined by 88% (from 2.3 down to 0.3 per 100,000 population) and visits to doctors declined by 59% (from 215 to 89 per 100,000 population). Hospitalisations and visits to doctors were reduced for all age groups, with the greatest reduction among infants.\(^3\)

Two varicella vaccines are registered currently in Australia - Varilrix and Varivax Refrigerated. From November 2005 to June 2006, 349,550 doses of varicella vaccine were administered to children under 7 years via the funded program.\(^4\)

Between 2000 and 2006, an estimated 1.3 million doses of varicella vaccine were distributed in Australia.\(^5\) During this period 342 reports of
adverse reactions following vaccination with varicella vaccine were received by ADRAC. Reported adverse events were mostly mild and transient, with the most common being rash, injection site reaction and pyrexia. Over the same period 115 reports have been received by ADRAC advising of incomplete protection from the disease by the varicella vaccine.

It should be noted that vaccination does not completely prevent varicella. In clinical trials breakthrough cases of chickenpox ranged from 0.6% to 3.9% of vaccinated individuals per year. In those who developed breakthrough chickenpox post-vaccination, the majority experienced mild disease.6

These data support varicella immunisation for public health protection. As with other live attenuated vaccines, varicella vaccine is not recommended for use in immunocompromised patients.

References:
1. MacIntyre CR, Chu CP, Burgess MA. Use of hospitalization and pharmaceutical prescribing data to compare the prevaccination burden of varicella and herpes zoster in Australia. *Epidemiology & Infection* 2003; 131: 675-682
4. Australian Childhood Immunisation Register. Medicare Australia Statistical Reporting
5. Sales data supplied as personal communication by GSK and MS&D pharmacovigilance staff

3. Drugs of Current Interest

Before approval and marketing, new drugs are studied extensively in clinical trials in order to establish efficacy and safety. However, at the time of first marketing, important safety issues may not be identified. Firstly, clinical trials do not routinely involve enough patients to establish details of rare adverse reactions (those occurring with a frequency of less than about 1 in 1000 patients). Secondly, there is often a lack of information on use in special populations such as pregnant women, children, the elderly, and those with coexisting illness. Thirdly, there may not be comprehensive data concerning drug interactions.

Once a drug is marketed, uptake in Australia can be significant; for example over 115,000 prescriptions for celecoxib and over 20,000 prescriptions for bupropion were dispensed in Australia in the first month of PBS subsidisation of each drug.

The initial months and years of a drug’s availability are crucial for gaining new information on safety in a large, diverse population. For this reason, ADRAC established its “Drugs of Current Interest” (DOCI) scheme in August 1990. This list generally includes all new drugs that are expected to be used widely in Australia, or those for which the Committee has identified an area of safety concern or uncertainty. Drugs normally remain on the list for 2 years, as this is the time period when the reporting of suspected adverse reactions is usually highest.

It should be noted that removal of a drug from the DOCI list does not necessarily mean that all safety concerns have been answered.

The DOCI scheme is a simple method to obtain safety information about marketed medicines. However, there is a need for properly-constructed postmarketing surveillance studies that address issues not addressed by clinical trials. It is hoped that such studies will become standard in the future.

The current DOCI list appears on the front of every Bulletin. Drugs on the list are reviewed regularly by the TGA and ADRAC for safety issues arising from spontaneous reports, the published literature, overseas regulatory agencies, or any other source.

ADRAC asks that all suspected adverse reactions to DOCIs be reported using the blue card scheme or via the TGA website.
WHAT TO REPORT? (you do not need to be certain, just suspicious!)

ADRAC encourages the reporting of all suspected adverse reactions to medicines, including vaccines, OTC medicines, herbal, traditional or alternative remedies. ADRAC particularly requests reports of:

*ALL suspected reactions to new drugs (see drugs of current interest, front page)
*ALL suspected drug interactions
*Suspected reactions causing
  • Death
  • Admission to hospital or prolongation of hospitalisation
  • Increased investigations or treatment
  • Birth defects

For blue cards
Reports of suspected adverse drug reactions are best made by using a prepaid reporting form ("blue card") which is available from the front of the "Schedule of Pharmaceutical Benefits" and the "Australian Medicines Handbook", or from the Adverse Drug Reactions Unit ☎ 02-6232-8744, or from the website: http://www.tga.gov.au/adr/bluecard.pdf

Reports can also be submitted electronically, by going to the TGA web site (http://www.tga.gov.au) and clicking on "report problems" on the left.

For further information from the ADRAC Secretariat:
☎ 1800 044 114    Fax: 02-6232-8392    Email: adrac@health.gov.au

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The Bulletin is also available on the Internet at: http://www.tga.gov.au/adr/aadrb.htm

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