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AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

VOLUME 23, NUMBER 6, DECEMBER 2004

- ☆ Use of SSRI antidepressants in children and adolescents
- ☆ Cardiovascular risk with the selective COX-2 inhibitors
- ☆ Propofol: danger of prolonged and high infusion rates in ICU

Please report **all** suspected reactions to these **Drugs of Current Interest**

Aripiprazole (Abilify)
Atomoxetine (Strattera)
Ezetimibe (Ezetrol)
Levetiracetam (Keppra)
Pimecrolimus (Elidel)
Reboxetine (Edronax)
Sibutramine (Reductil)

1. USE OF SSRI ANTIDEPRESSANTS IN CHILDREN AND ADOLESCENTS

(A statement by ADRAC dated 15 October 2004.[#])

The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has reviewed data on the safety and efficacy of SSRIs* in the treatment of major depressive disorder (MDD) and other psychiatric disorders in children and adolescents. The data reviewed has included the US FDA analysis in collaboration with a group at Columbia University.[†] ADRAC has also consulted again with the Royal Australian and New Zealand College of Psychiatrists and the Royal Australasian College of Physicians.

None of the SSRIs, and indeed no antidepressant, is currently approved in Australia for the treatment of MDD in children and adolescents (persons aged less than 18 years). Fluoxetine, but none of the other SSRIs, is approved in the US for MDD in young people without a specified lower age limit. Two of the SSRIs, fluvoxamine and sertraline, are approved in Australia for children and adolescents with obsessive compulsive disorder (OCD).

Assessment of the published and unpublished data available for SSRI use in children and adolescents indicates that there is evidence of an increased risk of suicidality, including suicidal ideation, suicide attempts and self-harm events, associated with each of the SSRIs.[1] The strongest association has been found with paroxetine and venlafaxine, but sertraline, citalopram and fluoxetine have also been implicated, with fluoxetine possibly having the smallest risk.[1,2] There are very few data for fluvoxamine.

Increases in suicidal ideation and behaviour during the early stages of antidepressant treatment are well-known clinical phenomena in adults. It is clear that these events can occur in children and adolescents as well. While the size of the increase compared to placebo is small, around 2 to 3 patients per 100, the effect is stronger with some SSRIs than others in young people.

In a recent study,[2] at the completion of therapy fluoxetine was beneficial for the treatment of depression in adolescents with moderate to severe symptoms of MDD. Treatment with fluoxetine plus cognitive behaviour therapy was more beneficial and decreased suicidal ideation compared with placebo by the end of the treatment period. *During therapy* with fluoxetine there was, however, an increase in some psychiatric adverse events (acts and ideation of suicide, self-harm, aggression, violence).

In general, clinical trials of SSRIs in children and adolescents have excluded severely depressed patients and have not adequately monitored participants for self-harm or suicide-related events. Other non-SSRI antidepressants have been subjected to even less scrutiny, and may be inefficacious and also associated with suicidality, as well as having other undesirable effects such as the toxicity in overdose of the tricyclics.

ADRAC recommends:

1. Any use of SSRIs in children and adolescents with MDD and other psychiatric conditions should be undertaken only within the context of comprehensive management of the patient. Management should include careful monitoring for the emergence of suicidal ideation and behaviour which may particularly develop early in therapy, or if therapy is interrupted or irregular because of poor compliance. Cognitive behaviour therapy, if it is available, may enhance the outcome in MDD.
2. The choice of an SSRI for a child or adolescent with MDD or other psychiatric condition should be made only after taking into account the recent evaluations of clinical trial data and the Australian product information (PI). Prescribers should be aware that the marketers of fluvoxamine and sertraline (indicated for OCD) advise against use in children and adolescents with MDD, and of citalopram, escitalopram, paroxetine, venlafaxine and fluoxetine warn or caution against use in patients aged less than 18 years for any indication.
3. Children and adolescents being treated for MDD with an SSRI should not have their medication ceased abruptly.

In addition, ADRAC asks that cases of emergent or worsening suicidal ideation or behaviour and self-harm in children or adolescents treated with an SSRI be reported to aid understanding of what might be an idiosyncratic response to the medication.

This ADRAC Statement is on the TGA web site at http://www.tga.gov.au/adr/adrac_ssri.pdf It has replaced the statement of 17 June 2004.

* The SSRI antidepressants included are citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, and the related medicine, venlafaxine.
† The FDA review also included mirtazapine which is not approved for use in children, bupropion which is not indicated as an antidepressant, and nefazodone which is no longer available in Australia.

References:
1. Mosholder AD. Suicidality in pediatric clinical trials of antidepressant drugs: comparison between previous analyses and Columbia University classification. Centre for Drug Evaluation and Research, Food and Drug Administration, 16 August 2004. http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-11-TAB09a-Mosholder-review.pdf (4 Oct 2004).
2. Treatment for Adolescents with Depression Study (TADS) Team. Fluoxetine, cognitive-behaviour therapy and their combination for adolescents with depression. *JAMA* 2004;292:807-20.

2. CARDIOVASCULAR RISK WITH THE SELECTIVE COX-2 INHIBITORS

At the end of September 2004, Merck Sharp and Dohme voluntarily withdrew from the market worldwide the selective COX-2 inhibitor, rofecoxib (Vioxx). This action was taken because the APPROVe study found an increase in the risk of cardiovascular events with rofecoxib 25mg daily compared with placebo.[1] An increased risk of thrombotic events with high dose (50mg daily) rofecoxib was already suspected.[2] The excess risk with rofecoxib 25mg, which was the maximum dose approved in Australia, emerged only after long-term use (> 18 months) in the APPROVe study.

A recent meta-analysis of studies involving rofecoxib found elevations in the risk of myocardial infarction at daily doses of 12.5mg, 25mg and 50mg and for treatment durations of < 6 months and ≥ 6 months. The elevation in risk was statistically significant for only the 50mg dose and for use for 6 months or more.[3]

The TGA is seeking long-term data on cardiovascular safety from the sponsors of all NSAIDs with some selective COX-2 inhibition approved for chronic use (celecoxib, Celebrex; etoricoxib, Arcoxia; lumiracoxib, Prexige; meloxicam, Mobic; valdecoxib, Valdyne). Concerning celecoxib, ADRAC has noted that the evidence suggests less risk than with rofecoxib,[2] and this is supported by a recent study.[4] However, studies involving celecoxib with adequate duration are still awaited.

ADRAC recommends that until the safety review of the COX-2 inhibitors is completed, it would be wise to consider that each of them, including celecoxib, may confer an increased risk of cardiovascular events. The cardiovascular risk profile of individual patients should be assessed before a selective COX-2 inhibitor is prescribed[2] and alternative agents considered if the risk is increased.

References
1. FDA Public Health Advisory: Safety of Vioxx, 30 Sep 2004. Internet http://www.fda.gov/cder/drug/infopage/vioxx/PHA_vioxx.htm (15 Nov 2004).
2. Rofecoxib, celecoxib and cardiovascular risk. *Aust Adv Drug Reactions Bull* 2003;22:19.
3. Jüni P, Nartey L, Reichenbach S et al. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet.* Internet http://image.thelancet.com/extras/04art10237web.pdf (published 5 Nov 2004).
4. Graham DJ, Campen D, Cheetham C, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with COX-2 selective and non-selective NSAIDs, 30 Sep 2004, Internet: http://www.fda.gov/cder/drug/infopage/vioxx/vioxxgraham.pdf (4 Nov 2004).

3. PROPOFOL: DANGER OF PROLONGED AND HIGH INFUSION RATES IN ICU

Propofol (Diprivan, Recofol) is indicated for induction of general anaesthesia and for sedation of adult ventilated patients. For on-going intensive care, the Australian product information advises that infusion rates of 1-3 mg/kg/hour should achieve satisfactory sedation and that infusion rates greater than 4 mg/kg/hour are not recommended. Elevated infusion rates and prolonged infusion are associated with a life-threatening syndrome, which may involve cardiac failure, arrhythmias, metabolic acidosis, rhabdomyolysis and renal failure.

In a case series, 7 of 67 ventilated adult head injury patients sedated with propofol died of myocardial failure associated with cardiac dysrhythmia, metabolic acidosis and/or hyperkalaemia.[1] All of these patients received propofol at a rate greater

than 5.0 mg/kg/hour for more than 58 hours. Patients who were treated at high infusion rates but did not develop the syndrome received sedation at this rate for shorter periods. A recent published Australian case report described a 31 year old head-injured male who died from ventricular fibrillation, metabolic acidosis, rhabdomyolysis and renal failure after infusion of 48g of propofol over 157 hours (mean rate 4.1 mg/kg/hour).[2]

In addition, ADRAC has received one report of lactic acidosis and one of torsade de pointes with propofol infusion in adult patients treated for about 24 hours at 30 and 100 mg/hour, respectively, both of which are considerably less than 4 mg/kg/hour. Although the main risks for the life-threatening propofol infusion syndrome are prolonged and high rates of infusion, these two reports illustrate that serious adverse events may also occur at low infusion rates for short periods.

References:
1. Cremer OL, Moons KGM, Bouman EAC et al. Long-term propofol infusion and cardiac failure in adult head-injured patients. *Lancet* 2001;357:117-8.
2. Ernest D, French C. Propofol infusion syndrome – report of an adult fatality. *Anaesth Intensive Care* 2003;31:316-319.

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", from the Adverse Drug Reactions Unit ☎ 02-6232-8386, 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 "adverse drug reaction reporting" on the right.

For further information from the ADRAC Secretariat:

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ISSN 0812-3837
The Bulletin is also available on the Internet at: http://www.tga.gov.au/adr/aadrb.htm

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