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AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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☆ Inadvertent paracetamol overdose
☆ Please report paediatric adverse reactions
☆ Screening guidelines for women exposed to DES in utero
☆ Retirement of Dr John McEwen

Please report all suspected reactions to these Drugs of Current Interest

Aripiprazole (Abilify) Levetiracetam (Keppra)
Atomoxetine (Strattera) Pimecrolimus (Elidel)
Ezetimibe (Ezetrol) Reboxetine (Edronax)
Fenofibrate (Lipidil) Teriparatide (Fortéo)
Iron sucrose (Venofer)
1. Inadvertent paracetamol overdose

Paracetamol is a remarkably useful simple analgesic with a good safety profile. Although intentional overdose, if left untreated, is a well known cause of hepatotoxicity, overdose associated with therapeutic use is an under-appreciated cause of serious liver injury. In a recently published Australian series, 9 of 29 cases of paracetamol-induced fulminant liver failure occurred with accidental overdose during the regular intake of paracetamol over a period of several days for the treatment of pain or febrile illness.\(^1\) Two additional articles have described a total of 10 Australian cases of paracetamol hepatotoxicity with therapeutic use in children given doses as low as 20 mg/kg/day.\(^2,3\)

In Australia the recommended dose for adults is 1g 4 hourly up to a maximum of 4 g/day, and for children and adolescents it is 15 mg/kg 4-hourly up to a maximum of 60 mg/kg/day (for 7-12 years maximum 2 g/day). Exceeding the recommended dose because of inadequate pain control, and failure to recognise the paracetamol content of other preparations used concurrently are potential causes of inadvertent overdose. There is a wide variety of products both OTC and by prescription that contain paracetamol.

In Australia OTC products containing paracetamol are required to carry the following warnings on the label:

- **Adults:** keep to the recommended dose. Don’t take this medicine for longer than a few days at a time unless advised to by a doctor.”
- **Children and adolescents:** Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor.”
- “If an overdose is taken or suspected, ring the Poisons Information Centre … or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage.”
- “Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist.”

These warnings became mandatory on 1 April 2005, and were introduced following a comprehensive review by the Therapeutic Goods Administration of the safety of paracetamol and an information campaign in 2003 to promote the safe and appropriate use of paracetamol.\(^4\) The paracetamol warning statements for labels have recently been updated in the US, also to reduce overdose in therapeutic use.\(^5\)

Although the data are still inconclusive, poor nutrition, chronic alcohol abuse and chronic liver disease may all predispose to paracetamol toxicity because of depletion of glutathione stores. Short term poor oral intake, such as may occur during a febrile illness or following surgery, may also increase the risk.

Severe hepatotoxicity related to overdose in the therapeutic setting may be associated with a poorer prognosis than intentional overdose, possibly because of delayed recognition and treatment. Patients typically present with marked elevations of serum transaminase concentrations, and the history of paracetamol ingestion may only be obtained on careful questioning. Presentation may be more than 24 hours since the last dose and plasma paracetamol may be low or undetectable by that time.

Health professionals are asked to reinforce the messages to avoid concurrent use of different paracetamol preparations, not to exceed the maximum daily dose, and not to use for more than a few days.\(^4\)

References
2. **Please report paediatric adverse reactions**

Much paediatric prescribing uses medicines in unapproved (or ‘off-label’) indications, which usually means that large scale clinical trials have not been conducted in the paediatric population and there may be little information on the efficacy or safety of the medicine used in this age group. Other than vaccine reports, only 3% of reports received by ADRAC in 2004 related to children aged 0-12 years, suggesting there may be under-reporting. Because of the use of medicines not approved in this age group, or for unapproved paediatric-specific indications, this under-reporting is an important issue that warrants attention by all health care professionals.

The adverse reaction profile of a medicine in children may be quite different from that in adults. For example, hepatic dysfunction with flucloxacillin and blood dyscrasias with cotrimoxazole very rarely occur in children, but serum sickness with cefaclor and serious skin reactions with lamotrigine are far more common in children than in adults. There may be many similar examples of differences in reaction profiles which are as yet unknown, including the safety of complementary medicines both in children and in the fetus when taken by pregnant women.

If paediatric adverse reaction reporting to ADRAC can be increased, the resulting central repository of adverse reactions will allow more effective analysis of reports for identification of adverse effects and risk factors. ADRAC has in the past published Bulletin articles on paediatric adverse effects and articles providing advice on the safe use of medicines in children, including vaccines for which ADRAC has a specific review process (see box). More reports will enable ADRAC to increase this service to those prescribing to children, general practitioners, community pharmacists, child health nurses and paediatricians, as well as to the children and their parents and caregivers.

**Bulletin articles pertaining to children since January 1998**

- Paradoxical reactions with midazolam in children – Feb 98
- Update on visual field constriction with vigabatrin – Feb 99
- Restriction of indications for cisapride – Dec 00
- Extensive limb swelling and DTPa booster – Aug 01
- Flucásone and adrenal crisis – Apr 03
- Maternal SSRI use and neonatal effects – Aug 03
- Meningococcal C vaccine: early experience is reassuring – Dec 03
- Corticosteroids should be used with long-acting β2-agonists – Jun 04
- Australian experience with pneumococcal conjugate vaccine – Oct 04
- Use of SSRI antidepressants in children and adolescents – Dec 04
- Pimecrolimus, skin cancer and lymphoma – Jun 05
- Suicidality with SSRIs: adults and children – Aug 05

* In November 2004, the Therapeutic Goods Administration hosted an Informal Consultation on Paediatric Adverse Reaction Reporting. This article is published as an outcome of that meeting.

3. **Screening guidelines for women exposed to DES in utero**

The NH&MRC approved new guidelines, *Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen Detected Abnormalities*, on 9 June 2005. These guidelines contain a section concerning women exposed in utero to diethylstilboestrol (DES). The guidelines advise that women with DES exposure should be offered annual cytological screening and colposcopic examination of both the cervix and the vagina. Readers of the guidelines are directed to the NSW Health website for more information on DES. The guidelines can be accessed at [http://www7.health.gov.au/nhmrc/publications/synopses/wh39syn.htm](http://www7.health.gov.au/nhmrc/publications/synopses/wh39syn.htm)

ADRAC has previously published information on the risks associated with DES exposure.1

Reference

1. ADRAC. The legacy of diethylstilboestrol (DES) from the 50s and 60s. *Aust Adv Drug Reactions Bull* 2004;23:10.
4. Retirement of Dr John McEwen

The publication of this Bulletin marks the end of an era for ADRAC with the retirement of Dr John McEwen. Dr McEwen was appointed Secretary of ADRAC in 1979 and held that position for 10 years. During that time, ADRAC became more involved with the dissemination of its findings to the wider community via the Bulletin and many publications in medical journals. Following stints in senior management with the TGA, as the Medical Director of CSL, and as the head of one of the clinical evaluations sections in the TGA, Dr McEwen returned to ADRAC as head of the revamped Adverse Drug Reactions Unit in 1999. The past 6 years have seen an expansion of the role of ADRAC to review all aspects of medicine safety in Australia together with an increase in the frequency of the Bulletin to 6 issues per year. Dr McEwen is recognised worldwide as a leader in the field of pharmacovigilance and has been in recent years, the public face of the TGA with involvement in the Pan recall and other issues. ADRAC members have greatly valued Dr McEwen’s support for its independent role in advising the TGA, and his considered and informed views on a wide range of issues. He will be greatly missed by ADRAC and the TGA. The committee wishes him well in his retirement.

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

For further information from the ADRAC Secretariat:
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