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AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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- ☆ Severe adverse reactions with intravenous immunoglobulin
 - ☆ Serious reaction reminders:
 - ...sodium valproate and fetal malformations*
 - ...cefaclor and serum sickness-like reactions in children*
 - ☆ Lignocaine with chlorhexidine gel and anaphylaxis
-

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

Duloxetine (Cymbalta)
Moxonidine (Physiotens)
Paliperidone (Invega)
Pramipexole (Sifrol)
Pregabalin (Lyrica)
Rosuvastatin (Crestor or Viacor)

Ranibizumab (Lucentis)
Rivaroxaban (Xarelto)
Sitagliptin (Januvia)
Strontium ranelate (Protos)
Varenicline (Champix)

1. Severe adverse reactions with intravenous immunoglobulin

Intravenous immunoglobulin, normal (human) (IVIG) is a plasma derived product used to treat a variety of deficiencies and disorders with an immune (or presumed immune) aetiology. IVIG preparations, including Intragam P, Sandoglobulin, and Octagam, have been available since the 1980s. Use worldwide and in Australia has more than doubled over the last decade¹, partly due to increasing use for “off-label” indications.

Nausea and vomiting are most commonly observed with IVIG, as are hypersensitivity reactions which may include anaphylaxis. Those with IgA deficiency have a higher risk of hypersensitivity to IVIG due to the presence of IgA antibodies. Less common but also serious reactions are aseptic meningitis, haemolysis and transfusion-related acute lung injury (one case has been reported in Australia and one in Canada²).

Recently, Health Canada highlighted an association between IVIG and thromboembolic events.³ They refer to reports of myocardial infarction or stroke during or shortly after the infusion. The pathogenesis of these events is not completely understood.³

To date we have received 356 reports of adverse reactions associated with IVIG: IVIG was the sole suspected agent in 319 (90%). 125 (35%) describe serious reactions, including 5 where the outcome was fatal due to: stroke/myocardial infarction, myocardial infarction, convulsions, hepatic and renal failure, and respiratory failure, respectively. In the fatal cases, patients generally had thrombogenic risk factors such as hypertension, obesity, increasing age, or past history of stroke.

2. Serious reaction reminders

...sodium valproate and fetal malformations

Sodium valproate is well known to cause fetal malformations and is classified as a Pregnancy Category D drug (*Drugs that have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects*).¹ Teratogenic risk appears to be dose-dependent and increases markedly at doses greater than 1100 mg/day in the first trimester.²

Many of the reports describe symptoms which may be consistent with a hypersensitivity reaction. These include 71 reports of rash, urticaria and/or pruritus, 33 of which also describe oedema and/or respiratory disorder. An additional 14 reports describe ‘anaphylaxis’ or ‘anaphylactoid reaction’.

We have also received substantial numbers of reports describing pyrexia (58), chills (41), haemolysis or anaemia (32), meningitis (20), neutropenia (12), hepatic disorders (11), and renal failure/impairment (8).

In some of the cases, the reactions, particularly those suggesting hypersensitivity, occurred during the IVIG infusion and improved with slowing or stopping the infusion.

Before and during the use of IVIG, assess if there are any pre-existing thrombogenic risk factors and monitor all patients closely during infusion. A slow infusion rate of IVIG should be considered for all patients with risk factors (as recommended in the PI).

References:

1. Criteria for the clinical use of intravenous immunoglobulin in Australia. Australian Health Ministers’ Conference. National Blood Authority. December 2007.
2. Case Presentation: Intravenous immune globulin – suspected association with transfusion-related acute lung injury. *Canadian Adverse Reactions Newsletter* Oct 2008; 18/4.
3. Intravenous immune globulin: myocardial infarction and cerebrovascular and thrombotic adverse reactions. *Canadian Adverse Reactions Newsletter* Jan 2008; 18/1.

Sodium valproate is mainly used to treat epilepsy but it is increasingly being prescribed to treat psychiatric disorders.

Since 1980, we have received 72 reports of babies born with malformations from mothers taking sodium valproate during pregnancy, including 18 of spina bifida, 4 of myelomeningocele and 13 of multiple malformations mainly involving the CNS. In most of these cases, sodium valproate was being used to treat epilepsy, but two recent

reports describe fetal spina bifida and myelomeningocele in babies born to mothers taking sodium valproate for bipolar disorder.

One of the cases reported to us has been described in correspondence to the *Australian and New Zealand Journal of Psychiatry*³ and serves to remind all prescribers that sodium valproate must be used with caution after careful consideration of the risk-benefit profile in women of child-bearing potential.

Women of child-bearing age prescribed sodium valproate for any indication should be informed about the potential risks of the drug, including teratogenesis, and should be strongly advised, and periodically reminded, to maintain adequate contraception while taking this drug. Routine folic acid supplementation is recommended but efficacy in the prevention of sodium valproate-related malformation is unproven.⁴

All pregnant women taking sodium valproate should be encouraged to join *The Australian Registry of Antiepileptic Drug Use in Pregnancy* (ph 1800 069 722) to assist in monitoring the use of this drug in pregnancy.

References:

1. ADEC. Prescribing medicines in pregnancy – An Australian categorisation of risk of drug use in pregnancy 4th edition (1999). Download this and updates from <http://www.tga.gov.au/docs/html/medpreg.htm>
2. Whitehall J & Smith J. Valproate and babies. *Aust NZ J Psychiatry* 2008; 42: 837.
3. Vajda FJ, O'Brien TJ, Hitchcock A, Graham J, Cook M, Lander C, Eadie MJ. Critical relationship between sodium valproate dose and human teratogenicity: results of the Australian register of anti-epileptic drugs in pregnancy. *J Clin Neurosci* 2004; 11: 854-83.
4. Lagrange AH. Folic acid supplementation for women with epilepsy who might become pregnant. *Nature Clin Pract* 2009; 5: 16-17.

3. Lignocaine with chlorhexidine gel and anaphylaxis

Lignocaine 2% gel with chlorhexidine 0.05% is an anaesthetic/antiseptic/disinfectant combination used as a lubricant for urology procedures and examination, and as symptomatic treatment of painful urethritis.

Since 1990, the TGA has received 19 reports of suspected adverse reactions to lignocaine with chlorhexidine gel. Eleven of these were of anaphylaxis. Some were life threatening, but there have been no fatalities. Four reports of anaphylaxis were received recently, from differing

...cefaclor and serum sickness-like reactions in children

The association between cefaclor and serum sickness-like reactions (SSLR), particularly in children, has long been recognised.¹ These reactions are characterised by a variety of rashes, which include urticaria or erythema multiforme, with or without angioedema, accompanied by arthritis/arthralgia, with or without fever.

The reactions are rare but occur more often after a second or subsequent course of treatment. Onset time is often a few days after cefaclor is commenced and signs and symptoms typically subside a few days after the drug is ceased. However, onset may also be delayed and occur 7-21 days after stopping cefaclor. Children are more susceptible than adults, but the underlying reasons are not clear.

Despite a steady decline of cefaclor prescriptions under the Pharmaceutical Benefits Scheme (PBS) and the cautionary note associated with the PBS entries (“*Caution: “Serum sickness-like reactions have been reported with this drug, especially in children”*”), we continue to receive about 10 reports per year of cefaclor-related SSLR in children.

If cefaclor must be prescribed to a child, the parents/caregivers should be advised to remain alert for the development of new or worsening symptoms that might indicate a hypersensitivity reaction to the drug and to contact their doctor immediately if there are concerns.

Reference:

1. ADRAC. Cefaclor in the young patient: arthritis and arthralgia. *Aust Adv Drug React Bull* 1995; 14 (3).

sources over a one month period. One of the patients was known to be allergic to chlorhexidine but the anaesthetist was not aware that the anaesthetic gel contained this substance.

The PI warns of the potential for anaphylaxis or other hypersensitivity reactions with both lignocaine and chlorhexidine. Users of local anaesthetic preparations should check which products contain chlorhexidine and are reminded of the risk of severe allergic reactions to medicines, even when applied topically.

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 website: <http://www.tga.gov.au/adr/bluecard.pdf> or from the Adverse Drug Reactions Unit ☎ 02-6232-8744.

Reports can also be submitted electronically, by going to the TGA website <http://www.tga.gov.au> and clicking on "report problems" on the left, by fax: 02-6232-8392, or email: ADR.Reports@tga.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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