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AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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- ☆ Hyponatraemia with SSRIs
 - ☆ Pregnancy despite depot medroxyprogesterone
 - ☆ Hepatic reactions with minocycline
 - ☆ Implanon and vaginal bleeding
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Please report **all** suspected reactions to these **Drugs of Current Interest**

Esomeprazole (Nexium)
Fondaparinux (Arixtra)
Galantamine (Reminyl)
Gatifloxacin (Tequin)
Lercanidipine (Zanidip)
Meloxicam (Mobic)
Mirtazapine (Avanza, Mirtazon, Remeron)
Moxifloxacin (Avelox)

Pioglitazone (Actos)
Pramipexole (Sifrol)
Reboxetine (Edronax)
Rosiglitazone (Avandia)
Sibutramine (Reductil)
Tadalafil (Cialis)
Tegaserod (Zelmac)

1. HYPONATRAEMIA WITH SSRIs

ADRAC has now received a total of 311 reports of hyponatraemia involving SSRIs and venlafaxine (see table).¹ In 67 of these reports, it was indicated that the patient had the syndrome of inappropriate ADH secretion (SIADH) although serum and/or urine osmolality results were not included in every case. As a group, the SSRIs account for about one-quarter of all reports of hyponatraemia received by ADRAC, and are second to diuretics as the group most commonly associated with hyponatraemia.

Table: Reports of hyponatraemia with the SSRIs and venlafaxine

Drug	Total Reports	Reports of hyponatraemia
Citalopram	388	35
Fluoxetine	1148	50
Fluvoxamine	142	3
Paroxetine	1587	46
Sertraline	4503	130
Venlafaxine	695	47
Total		311

In more than two-thirds of the 311 reports, the SSRI was the only suspected drug and three-quarters of the reports involved females. A small proportion (14%) identified concurrent use of a diuretic. The median patient age was 77 years (range 13 to 99); about 85% were older than 60 years. Onset was usually within the first month of treatment. In many of the reports hyponatraemia was the sole abnormality reported, with the median serum sodium nadir at 120 (range 113 to 133) mmol/L. Other reports listed neuropsychological symptoms such as confusion, convulsions, fatigue, delirium, syncope, somnolence, agitation, dizziness and hallucinations. Some patients experienced other behavioural changes such as aggressive reactions, personality disorders or depersonalisation. Changes in pulse or blood pressure occasionally occurred.

2. PREGNANCY DESPITE DEPOT MEDROXYPROGESTERONE

ADRAC has received 27 reports of women becoming pregnant despite using depot medroxyprogesterone products (Depo-Provera, Depo-Ralovera) for contraception. In 10 of the cases, the woman was confirmed as becoming pregnant 2-10 weeks after administration of the drug. An interaction with carbamazepine may have been a

factor in two of these cases. In another nine cases, the injections were given late or at borderline times.

These depot progesterone contraceptives have a high level of efficacy.¹ However, prescribers and other health care professionals who administer

In about two-thirds of cases, full recovery followed withdrawal of the SSRI and fluid restriction. Three cases had a fatal outcome related to hyponatraemia. Other patients had not recovered or the outcome was unknown at the time of reporting.

The pattern of ADRAC reports is consistent with published findings suggesting that hyponatraemia with SSRIs is more frequent in the elderly, particularly females, and onset is mostly during the first 30 days after commencing an SSRI.² SIADH appears to be part of the mechanism of hyponatraemia with the SSRIs, and inhibition of serotonin reuptake may be associated with a central increase in ADH release and hence induction of SIADH.³

A recent Australian study of elderly psychiatric patients found that use of an SSRI or venlafaxine was associated with a 3.5-fold increase in the risk of hyponatraemia after controlling for age, sex, depression status, use of other drugs associated with hyponatraemia and seriousness of physical disease.⁴

Neuropsychological symptoms developing in the first month of SSRI or venlafaxine use should prompt measurement of serum electrolytes. Elderly females and patients taking diuretics are at added risk.

References

- 1 ADRAC. Selective serotonin reuptake inhibitors and SIADH. *MJA* 1996;164:562
- 2 Liu B, Mittmann N, Knowles S et al. Hyponatraemia and the syndrome of inappropriate antidiuretic hormone associated with the use of selective serotonin reuptake inhibitors. *Can Med Assoc J* 1996;155 (5):519-527
- 3 Fisher A, Davis M, Croft-Baker J et al. Citalopram-induced severe hyponatraemia with coma and seizure. *Adv Drug React Toxicol Rev* 2002;21:179-87
- 4 Kirby D, Harrigan S, Ames D. Hyponatraemia in elderly psychiatric patients treated with selective serotonin reuptake inhibitors and venlafaxine. *Internat J Ger Psychiatry* 2002;17:231-7

these drugs need to avoid the following situations which contribute to the risk of contraceptive failure:

- Incorrect timing of the injection – injections must be commenced during the first five days after the onset of a normal menstrual period, within five days postpartum if not breastfeeding or, if breastfeeding, at six weeks postpartum, after having excluded pregnancy. Injections are given at 3-monthly intervals, no more than 14 weeks apart. If the interval is greater than 14 weeks, a pregnancy test should be conducted prior to administration.
- Failure to properly suspend the microcrystals by not adequately shaking the vial. Storing

vials on their side may allow the microcrystals to cake and fail to suspend when shaken.

- Failure to give the full dose – inadequate drawing up or full dose not injected.
- Incorrect injection technique with deposition of the suspension in tissues superficial to the muscles.
- Incorrect drug being administered – there has been one case of Depo-Medrol being used instead of Depo-Provera.

Reference

1. Borgatta L, Murthy A, Chuang C et al. Pregnancies diagnosed during Depo-Provera use. *Contraception* 2002;66:169-72.

3. HEPATIC REACTIONS WITH MINOCYCLINE

Minocycline is an effective long-term treatment for severe acne, but it is associated with serious adverse reactions, including rare cases of hepatic dysfunction. In one study the incidence of hepatic reactions in new users was one case/10,000 person-months.¹

ADRAC has received 42 reports of hepatic reactions with minocycline including 21 of hepatitis. It was the only drug taken by most of these patients, and was used for acne by 28. Fifteen patients were under 21 years of age. Where liver enzyme results were provided, they showed a hepatocellular pattern (12) more often than a cholestatic (3) or mixed picture (2). Time to onset was provided in 13 reports and suggested that cholestatic reactions occurred earlier (≤ 4 weeks) than hepatocellular damage (usually after months or years). Of the 42 cases, 25 had recovered by the time of reporting, usually in less than 12 weeks. None of the patients died or required liver transplantation.

A published case series suggests that hepatic reactions with minocycline may present either with features of a hypersensitivity syndrome (onset

within 35 days) or resemble autoimmune chronic active hepatitis (onset after months or years).² Despite well-documented reports, no ADRAC cases conformed to the criteria for a hypersensitivity syndrome. However, five reports were suggestive of an autoimmune reaction. All cases had antinuclear antibodies, and one had other features of lupus erythematosus. A time to onset of 11 or 12 months was specified in two cases.

Other serious adverse reactions associated with minocycline include CNS effects, skin discolouration and benign intracranial hypertension. Prescribers are particularly advised to note that hepatitis developing in a patient on long-term minocycline may be indistinguishable from autoimmune hepatitis both serologically and histologically. Discontinuation of minocycline usually results in complete recovery.

References

- 1 Seaman HE, Lawrenson RA, Williams TJ et al. The risk of liver damage associated with minocycline: a comparative study. *J Clin Pharmacology* 2001;41(8):852-60.
- 2 Lawrenson RA, Seaman HE, Sundstrom A et al. Liver damage associated with minocycline use in acne: a systematic review of the published literature and pharmacovigilance data. *Drug Safety* 2000;23:333-49.

4. IMPLANON AND VAGINAL BLEEDING

Since August 2001, ADRAC has received 130 adverse reaction reports for Implanon (subdermal etonogestrel contraceptive implant), including 37 reports of vaginal bleeding, most of which described prolonged bleeding (duration 2-26 weeks; median 8 weeks). The bleeding generally

started soon after insertion, but the time to onset was up to 16 weeks. Thirty-three of the 37 patients required implant removal. One patient was hospitalised, and transfused 4 units of packed red blood cells.

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IMPLANON (cont)

In a published 3-year study, 2.8% of patients experienced heavy or prolonged bleeding with Implanon.¹

Unacceptable vaginal bleeding may occasionally

occur with Implanon, and often requires implant removal.

Reference

1. Croxatto HB. Clinical profile of Implanon: a single-rod etonogestrel contraceptive implant. *Eur J Contraception Reprod Health Care* 2000; 5(Suppl 2): 21-8.

WHAT TO REPORT? (you do not need to be certain, just suspicious!)

The Adverse Drug Reactions Advisory Committee (ADRAC) encourages the reporting of all **suspected** adverse reactions to drugs and other medicinal substances, including herbal, traditional or alternative remedies. The reporting of seemingly insignificant or common adverse reactions may highlight a widespread prescribing problem.

The Committee particularly requests reports of:

*ALL suspected reactions to NEW DRUGS, especially **DRUGS OF CURRENT INTEREST**

*ALL suspected drug interactions

*Reactions to other drugs which are suspected of significantly affecting a patient's management, including reactions suspected of causing

- Death
- Danger to life
- Admission to hospital
- Prolongation of hospitalisation
- Absence from productive activity
- Increased investigational or treatment costs
- Birth defects

Reports of suspected adverse drug reactions are best made by using a prepaid reporting form ("blue card") which is available from the Adverse Drug Reactions Unit



02-62328386, or from the website: <http://www.health.gov.au/tga/adr/index.htm>

Tear-out blue cards can also be found at the front of the "Schedule of Pharmaceutical Benefits" and the "Australian Medicines Handbook".

Reports can also be submitted electronically, by clicking on "Online Services" at the TGA website (<http://www.health.gov.au/tga>) and following the links.

Further information can be obtained from the medical and scientific staff in the ADRAC Secretariat:



1800 044 114

Fax:

02-62328392

Email: adrac@health.gov.au

(Problems with therapeutic devices should be reported on 1800-809361)

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

All correspondence to be addressed to: The Secretary, Adverse Drug Reactions Advisory Committee, PO Box 100, Woden, ACT, 2606