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# AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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- ☆ Sildenafil — three years experience
- ☆ Haemorrhagic cystitis with ticarcillin in cystic fibrosis patients
- ☆ Venous thromboembolism with third generation oral contraceptives and cyproterone

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

Bupropion (Zyban)  
Galantamine (Reminyl)  
Gatifloxacin (Tequin)  
Lercanidipine (Zanidip)  
Meloxicam (Mobic)  
Mirtazapine (Avanza, Remeron)  
Moxifloxacin (Avelox)  
Oseltamivir (Tamiflu)  
Oxcarbazepine (Trileptal)  
Pioglitazone (Actos)

Quetiapine (Seroquel)  
Reboxetine (Tegaserod)  
Risedronate (Actonel)  
Rivastigmine (Exelon)  
Rofecoxib (Vioxx)  
Rosiglitazone (Avandia)  
Sibutramine (Reductil)  
Tegaserod (Zelmac)  
Zolpidem (Stilnox)

## 1. SILDENAFIL — THREE YEARS EXPERIENCE

Sildenafil (Viagra) has now been available in Australia for over 3 years. During that time ADRAC has received 773 reports for sildenafil with it as the only suspected drug in 741. Most of these reports describe reactions that are relatively minor in nature and are consistent with the pharmacology of the drug and the adverse effects observed during clinical trials (see Table 1).

There have been, however, 20 reports describing myocardial infarction which included 4 with a fatal outcome. Nine of the 20 patients had established cardiovascular disease or diabetes, or were at high risk of cardiovascular disease, and one was taking concomitant nitrates. There have also been 26 other reports of chest pain and 10 other reports which described a fatal outcome: 6 sudden unexplained deaths, 2 strokes and 2 subarachnoid haemorrhages. The temporal relationship to the ingestion of sildenafil was often not reported and in only 23 of these 56 cases could it be inferred that the event occurred within 6 hours of the use of the drug.

Because ingestion of sildenafil occurs in the context of sexual intercourse and, in some cases, underlying coronary disease, the contribution of sildenafil to cardiac events is difficult to assess. Information on prior risk factors and accurate details on drug ingestion and timing of the adverse reaction are often lacking. Resolution of the role of sildenafil requires robust epidemiological studies, however a recent publication which shows no evidence for a higher incidence of fatal myocardial infarction or ischaemic heart disease among users of sildenafil

provides some reassurance that sildenafil may not be a primary cause of cardiovascular events.<sup>1</sup>

Adverse Reaction	Number of Reports
Headache	233
Flushing	139
Abnormal vision	65
Therapeutic inefficacy	51
Rhinitis	42
Chest pain	34
Dizziness	31
Dyspepsia	28
Nausea	27
Myocardial infarction	20
Abdominal pain	16
Palpitation	16
Priapism	16

Prescribers are reminded that the drug is contraindicated in men for whom sexual intercourse is inadvisable such as those with severe cardiovascular disease, established cardiac failure and unstable angina pectoris. The possibility of undiagnosed cardiovascular disorders in men with erectile dysfunction should be considered before prescribing. Sildenafil has been shown to potentiate the hypotensive effects of both acute and chronic nitrate administration and, therefore, its coadministration with nitrates in any form, either regularly or intermittently, is contraindicated.

### Reference:

1. Shakir SAW, Wilton LV, Boshier A, Layton D, Heeley E. Cardiovascular events in users of sildenafil: results from first phase of prescription event monitoring in England. *BMJ* 2001; 322: 651-2.

## 2. HAEMORRHAGIC CYSTITIS WITH TICARCILLIN IN CYSTIC FIBROSIS PATIENTS

Only 58 reports of haemorrhagic cystitis, characterised by dysuria and haematuria, have been reported to ADRAC since 1972. The reaction is well known in association with cyclophosphamide (22 reports) and tiaprofenic acid (8) but it may not be appreciated that ticarcillin, a semisynthetic antibacterial agent derived from penicillin is also an important cause. Ticarcillin either alone (which is no longer available) or in combination with clavulanic acid (Timentin) is registered for intravenous administration in the treatment and prophylaxis of many infections including those that complicate cystic fibrosis. Fifteen reports of haemorrhagic

cystitis with ticarcillin or ticarcillin-clavulanic acid have been received by ADRAC since 1980 and describe 9 males and 6 females aged 2 to 19 years. All had cystic fibrosis. Onset of the reaction occurred from four hours to 3 weeks after starting ticarcillin.

Three reports documented recurrence of the haemorrhagic cystitis on rechallenge. In one case, cystitis occurred 11 days after the first course in a girl at 13 years of age, 8 days after the second course at 16 years and 4 hours after the first dose of the third course at 18 years of age. Three reports included ultrasound evidence of bladder

wall thickening. Ticarcillin is known to increase bleeding time and in the two patients where this was tested, it was normal in one and prolonged in the other. Almost all patients recovered quickly after withdrawal of ticarcillin. There are two publications in the literature describing 3 children with cystic fibrosis who developed this reaction after the use of ticarcillin.<sup>1,2</sup>

Ticarcillin is a rare cause of haemorrhagic cystitis. Health professionals should be aware that

prompt recognition and withdrawal of ticarcillin usually results in rapid recovery. It appears from the reports to ADRAC and elsewhere that paediatric patients with cystic fibrosis are those most at risk.

#### References:

1. Marx CM, Alpert SE. Ticarcillin-induced cystitis. Cross reactivity with related penicillins. *Am J Dis Child* 1984; 138: 670-2.
2. Relling MV, Schunk JE. Drug-induced haemorrhagic cystitis. *Clin Pharm* 1986; 5: 590-7.

### 3. VENOUS THROMBOEMBOLISM WITH THIRD GENERATION ORAL CONTRACEPTIVES AND CYPROTERONE

#### Third Generation Oral Contraceptives

Venous thromboembolism (VTE) is a recognised complication of oral contraceptives. For a number of years it has been debated whether “third generation” (containing desogestrel or gestodene) combined oral contraceptive pills (OCP) carry a higher risk of VTE than “second generation” OCP (containing levonorgestrel or norethisterone). A number of independent studies addressing the issue have been published.<sup>1,2</sup> The European Agency for the Evaluation of Medicinal Products (EMA) released its final position statement in September 2001 which indicates a “small increased risk of venous thromboembolism” with OCPs containing desogestrel or gestodene compared with second generation OCPs.<sup>3</sup> The overall conclusions of both the EMA and an earlier statement from New Zealand Medsafe in 1996<sup>4</sup> are as follows:

- VTE is a rare adverse effect of all combined oral contraceptives. The level of risk is low (and lower than in pregnancy) and the benefits of the use of OCPs compare favourably with the risks. The risks of VTE are highest in the first year of use.
- The risk of developing VTE with third generation OCPs is about twice that of second generation OCPs.
- It has been estimated that for every 10,000 women on a second generation OCP for a year, 2 women would be expected to develop a clot. For third generation OCPs, that figure is estimated to be about 3 to 4 women per 10,000 per year.
- Major risk factors for VTE include inherited thrombophilia, obesity, smoking, old age, trauma, pregnancy, surgery, and

immobilisation. (see article in the Australian Prescriber accompanying this Bulletin).<sup>5</sup>

Third generation OCPs marketed in Australia are shown in Table 2 (see back page). These products are not extensively used in Australia.

#### Combined Cyproterone Products

New Zealand Medsafe has also released a statement concerning oral contraceptives containing cyproterone.<sup>6</sup> The conclusion of its review is that:

- The risk of developing VTE with cyproterone OCPs is about 4 times that of second generation OCPs.
- It has been estimated that for every 10,000 women on an OCP containing cyproterone, about 8 women per year would be expected to develop a clot.

In Australia, products containing low dose cyproterone (2 mg) combined with ethinylloestradiol (see Table 2) are not indicated for contraception but for treatment of signs of androgenisation in women. These include severe acne where prolonged oral antibiotics or local treatment alone has not been successful, and idiopathic hirsutism of mild to moderate degree. These products will also provide effective oral contraception in this patient group but they are not available on the PBS.

ADRAC suggests that all women being prescribed combined oral contraceptives or combined cyproterone products should be advised of the benefits and risks. Each woman should be assessed carefully for inherent or pre-existing risk factors, including family history. For cyproterone, the indications for use should be followed.

References: (see back page)

Table 2: Combined Oral Contraceptive and Cyproterone Products Available in Australia		
Second Generation OCPs	Levonorgestrel	Norethisterone
	Biphasil, Levlen, Loette, Logynon, Microgynon, Monofeme, Nordette, Nordiol, Sequilar, Trifeme, Triphasil, Triquilar	Brevinor, Improvil, Norimin, Norinyl, Synphasic
Third Generation OCPs	Desogestrel	Gestodene
	Marvelon	Femoden, Minulet, Tri-Minulet, Trioden
Cyproterone	Brenda, Diane, Juliet	

#### References:

1. Committee on Safety of Medicines/Medicines Control Agency. Combined oral contraceptives containing desogestrel or gestodene and the risk of venous thromboembolism. *Curr Problems Pharmacovigilance* 1999; 25: 12.
2. Spitzer W, Lewis MA, Heinemann LAJ, Thorogood M, MacRae KD. Third generation oral contraceptives and risk of venous thromboembolic disorders: an international case-control study. *BMJ* 1996; 312: 83-88.
3. The European Agency for the Evaluation of Medicinal products, Committee for Proprietary Medicinal Products (CPMP). Position Statement: CPMP concludes its assessment of 'third generation' combined oral contraceptives and the risk of venous thromboembolism. Available from:

<http://www.emea.eu.int/pdfs/human/regaffair/0225001en.pdf> (viewed 30 January 2002).

4. Medsafe Editorial Team. **The risk of venous thromboembolism with third generation oral contraceptives.** Available from <http://www.medsafe.govt.nz/Profes/PUarticles/contraceptivesJuly96.htm> (viewed 4 March 2002).

5. Weisberg E. Contraception, hormone replacement therapy and thrombosis. *Aust Prescr* 2002; 25: 57-59.


6. Savage R. Venous thromboembolism with Diane 35 and Estelle 35. Available from <http://www.medsafe.govt.nz/Profes/PUarticles/VTEwithCPA.htm> (viewed 9 April 2002).

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

- 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, or 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), the front of the "Schedule of Pharmaceutical Benefits", and in the "Australian Medicines Handbook".

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

 1800 044 114  
Fax: 02-62328392

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

The Bulletin is also available on the Internet at:

<http://www.health.gov.au/tga/docs/html/aadrbltn/aadrbidx.htm>

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