The legacy of diethylstilboestrol (DES) from the 50s and 60s

Parecoxib – one shot only

Corticosteroids should be used with long-acting $\beta_2$-agonists

Atypical antipsychotics and hyperglycaemia

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

- Aripiprazole (Abilify)
- Ezetimibe (Ezetrol)
- Fondaparinux (Arixtra)
- Galantamine (Reminyl)
- Lercanidipine (Zanidip)
- Levetiracetam (Keppra)
- Pioglitazone (Actos)
- Reboxetine (Edronax)
- Rosiglitazone (Avandia)
- Sibutramine (Reductil)
- Tegaserod (Zelmac)
1. THE LEGACY OF DIETHYLSTILBOESTROL (DES) FROM THE 50s AND 60s

Diethylstilboestrol, or DES (also known as stilboestrol), is a synthetic oestrogen which was used more than three decades ago to prevent miscarriage.

In 1971, an association was demonstrated between in utero exposure to DES, and the development of a rare cancer, clear cell adenocarcinoma (CCAC) of the vagina, in exposed daughters (‘DES daughters’) who were diagnosed at ages up to 22 years.1 The lifetime incidence of CCAC in these women has been estimated at about 1 per 1000.2 Considerable publicity was given to this association and it is believed that use of DES to prevent miscarriage in Australia stopped in the early 1970s.3,4,5 ADRAC is aware of 15 Australian cases.*

Since the 1971 study other adverse effects associated with DES have been identified in DES daughters:

- vaginal and cervical adenosis is very common, with reported incidence as high as 90%
- other histological and structural reproductive tract abnormalities have been reported (incidences range from 18% - 58%)
- occurrence of cervical and vaginal dysplasia, squamous cell carcinoma-in-situ, and high grade squamous intraepithelial lesions is about doubled
- infertility rates are slightly increased
- pregnancy complication rates, such as premature deliveries, miscarriages, ectopic pregnancies and pre-eclampsia are increased

For the women who took DES (‘DES mothers’), a small increase in the rate of breast cancer has been reported. The sons exposed to DES in utero (‘DES sons’) have an increased occurrence of epididymal cysts. Careful surveillance on the next generation is being maintained (‘DES grandchildren’), but there is no clear evidence to date of adverse effects in the children of DES daughters or sons.

Australian guidelines for cervical and breast screening for all women are being reviewed. In the interim, any women with a history of exposure to DES (mothers and daughters) should, at least, follow the current national cervical and breast screening recommendations. Daughters exposed in utero should be reviewed by a gynaecologist, if they have not been previously.

*Eight Australian cases of CCAC are recorded in the ADRAC database and 7 in a US registry – Registry for Research on Hormonal Transplacental Carcinogenesis, University of Chicago.

Sources of further information

- The website of the US Centers for Disease Control has a very extensive set of materials about DES for health professionals and consumers: http://www.cdc.gov/des
- In Victoria, there is a DES follow-up clinic at the Royal Women's Hospital; contact telephone number (03) 9344 2000.

References:
4. ADEC. Stilboestrol and adenocarcinoma of the vagina. MJA 1972, Sept 9: 622-623

2. PARECOXIB – ONE SHOT ONLY

Parecoxib sodium (Dynastat) is a recently marketed parenteral COX-2 inhibitor which is approved for a single peri-operative dose for the management of post-operative pain. The Australian Drug Evaluation Committee recommended approval for parecoxib at a single dose only, because of concerns about the safety of multiple doses.

ADRAC has, to date, received 20 reports of adverse reactions associated with parecoxib, and 13 of these involved renal impairment with elevated creatinine and/or oliguria, including four cases of acute renal failure. Multiple doses of parecoxib were given in six cases, with patients receiving up to five doses. The other seven patients received only one dose, but two had risk factors:
one was also taking a diuretic and an angiotensin II receptor antagonist; and the other had pre-existing mild diabetic nephropathy. The patients were aged 41-78 (median 66) years.

It is clear that parecoxib can cause renal impairment and the risk is increased with multiple doses. Those patients most at risk are those mentioned in the Precautions section of the product information, including those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly.

3. CORTICOSTEROIDS SHOULD BE USED WITH LONG-ACTING $\beta_2$-AGONISTS

Long-acting bronchodilators (salmeterol [Serevent], eformoterol [Foradile, Oxis]) should only be used with concomitant daily oral or inhaled corticosteroids, as described in the approved indication for the products, and in current guidelines for the treatment of asthma, such as those prepared by the National Asthma Council.1

The results of the unpublished Serevent Multicenter Asthma Research Trial (SMART) have reinforced the importance of this advice.2,3 The SMART study was a large (around 26,000 subjects) post-marketing randomised trial of salmeterol versus placebo, in which participants were permitted to continue with their usual asthma therapy. The US study was stopped early because of a higher number of asthma-related life-threatening experiences, including death, in the salmeterol group than the placebo group. While the difference between treatment groups was not significant overall, when the analysis was restricted to patients who were not also on regular corticosteroid therapy, there was a statistically significant greater risk of asthma-related death with salmeterol than with placebo. African American patients in the study also had a significantly higher rate of asthma-related events, including death, with salmeterol than with placebo. Only 38% of these patients were using inhaled corticosteroids.3

Corticosteroids control the inflammation associated with asthma. Use of long-acting $\beta_2$-agonists without corticosteroid treatment can mask the symptoms of worsening inflammation until a critical point is reached and serious bronchospasm occurs.

References

4. ATYPICAL ANTIPSYCHOTICS AND HYPERGLYCAEMIA

Although schizophrenic patients appear to have a higher incidence of diabetes than the general population, a recent US study concluded that the risk of developing type II diabetes was approximately 1.5 times greater in patients taking olanzapine, risperidone, or quetiapine than in those taking conventional antipsychotics.1 Previous studies had shown an increased risk with clozapine use.2 Significant weight gain may be seen with these drugs (particularly clozapine and olanzapine), and may compound any pre-existing risk of diabetes, but hyperglycaemia and diabetes have been reported in the absence of weight gain. The mechanism of this adverse effect is unknown, but may be via either increased insulin resistance or decreased insulin secretion due to direct pancreatic $\beta$-cell inhibition via the serotonin 5-HT$_{1A}$ receptor. Lipid abnormalities (increased LDL and triglycerides and decreased HDL) have also been reported in association with the use of these drugs.2

**Table:** ADRAC reports of impaired glucose metabolism with the atypical antipsychotics

<table>
<thead>
<tr>
<th></th>
<th>Clozapine</th>
<th>Olanzapine</th>
<th>Risperidone</th>
<th>Quetiapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>52</td>
<td>19</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Other reports of impaired glucose metabolism</td>
<td>55</td>
<td>13</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Weight increase</td>
<td>51</td>
<td>66</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Total reports</td>
<td>2826</td>
<td>922</td>
<td>510</td>
<td>144</td>
</tr>
</tbody>
</table>

ADRAC has received reports of hyperglycaemia and new onset diabetes with four of the atypical antipsychotics, clozapine, olanzapine, quetiapine, and risperidone (see Table).
In the reports to ADRAC of diabetes, the median age was 42 (range 30-56) years for olanzapine, and 38 (range 17-70) years for clozapine. The median time to onset was 13 months (range 2 days - 4 years) for olanzapine, and 25 months (range 20 days - 8 years) for clozapine. Olanzapine was the sole suspected drug in 17 of the 19 reports, and clozapine in 49 of the 52 reports.

In some of the reports to ADRAC, recovery followed withdrawal of the antipsychotic, but in other reports, continuing treatment with an antidiabetic agent was required even after the antipsychotic was withdrawn.

Diabetic patients who are starting atypical antipsychotics should be monitored closely for worsening of diabetic control. Patients considered at particular risk of developing diabetes, for example because of obesity, hypertension, hyperlipidaemia, or family history of diabetes, should have routine periodic fasting blood glucose measurements. A consensus conference suggested a measurement at 3 months and annually thereafter. It was also suggested that a weight gain of more than 5% should prompt consideration of a change of drug. All patients should be monitored for the symptoms of hyperglycaemia, including thirst, polyuria, or weakness, and should have blood glucose measured if any of these symptoms appear. If diabetes develops a change of drug should be considered.

Please continue to report these reactions to ADRAC, including any such reactions associated with the use of the two newest antipsychotics, ziprasidone and aripiprazole. The propensity of these two agents to cause hyperglycaemia is as yet unclear.

References

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

Reports of suspected adverse drug reactions are best made by using a prepaid reporting form ("blue card") which is available from at the front of the "Schedule of Pharmaceutical Benefits" and the "Australian Medicines Handbook", or from the Adverse Drug Reactions Unit ☏ 02-62328386, or from the website: [http://www.tga.gov.au/adr/bluecard.pdf](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](http://www.tga.gov.au)) and clicking on “adverse drug reaction reporting” on the right.

Further information can be obtained from the ADRAC Secretariat:
☎ 1800 044 114 Fax: 02-62328392 Email: adrac@health.gov.au

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