Rituximab and progressive multifocal leukoencephalopathy

Implanon: interactions and failure of contraception

Atypical antipsychotic agents and extrapyramidal side effects

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Please report all suspected reactions to these Drugs of Current Interest

Atomoxetine (Strattera) Ranibizumab (Lucentis)
Ezetimibe/Simvastatin (Vytorin) Rosuvastatin (Crestor / Viacor)
Lumiracoxib (Prexige) Strontium ranelate (Protos)
Moxonidine (Physiotens) Ziprasidone (Zeldox)
Pregabalin (Lyrica)
1. Rituximab and progressive multifocal leukoencephalopathy

ADRAC has received a report of the rare neurological disease, progressive multifocal leukoencephalopathy, associated with the use of rituximab (Mabthera).1

Rituximab is an immunosuppressant available in Australia since 1998 for the treatment of certain types of non-Hodgkin’s lymphoma. Its indications were extended in December 2006 to include use with methotrexate for the treatment of severe active rheumatoid arthritis in patients not responding to, or unable to take, a tumour necrosis factor antagonist.

In December 2006 the FDA issued an advisory noting that two patients had died after treatment with rituximab for systemic lupus erythematosus.2 The cause of death was progressive multifocal leukoencephalopathy (PML), a viral infection of the brain caused by reactivated JC virus. JC virus is a human polyomavirus that causes widespread infection in childhood and is latent in about 80 percent of adults.2

PML is a rare but devastating disease, occurring in fewer than 1 per 1500 patients with lymphoma treated with rituximab in clinical trials. No cases were reported in approximately 3000 patients with rheumatoid arthritis receiving rituximab.3

Symptoms of PML include mental deterioration, confusion, vision loss, difficulty speaking, and loss of balance. PML usually results in death or severe disability.

There is no known effective treatment other than to stop medicines that are interfering with the immune system.

In the case reported to ADRAC, a patient with Waldenstrom’s Macroglobulinemia presented with altered vision and a new left homonymous hemianopia one month after commencing rituximab. He had a complicated history and had received other immunosuppressive treatment including fludarabine, corticosteroids and irradiation. He died 5 months later, with widespread lesions of PML found at autopsy.1

Although rituximab is a highly specialised medicine, its use is increasing and it is possible that patients taking rituximab will present to GPs when new symptoms develop. Patients treated with rituximab who present with new neurological signs or symptoms should be referred for evaluation. The Precautions/spontaneous reporting sections of the rituximab Product Information have been recently updated to include information relating to PML.

References:

2. Implanon: interactions and failure of contraception

Hepatic enzyme inducing medicines can reduce the efficacy of contraceptives, including implantable contraceptives, leading to unintended pregnancy.

Medicare Australia data indicate that 370,173 etonogestrel-containing contraceptive implants (Implanon) have been dispensed since 2001. The ADRAC database contains 594 reports concerning Implanon, 32 of which describe a suspected interaction between Implanon and another medicine, resulting in unintended pregnancy.

Medicines implicated in a possible interaction with Implanon leading to contraceptive failure include carbamazepine (26), phenytoin (4), methylphenobarbital (1) and rifampicin (1). All but 1 of these interactions involved medicines used to treat epilepsy. The 4 interacting medicines are potent inducers of CYP3A4 and other phase I and phase II enzyme systems in the liver. This enzyme induction is likely to reduce plasma concentrations of etonogestrel which, similar to other contraceptive steroids, is catalysed by CYP3A4.

Other medicines likely to interact with etonogestrel and thus possibly reduce its contraceptive effect or lead to breakthrough bleeding include primidone, oxcarbazepine, rifabutin, griseofulvin and products containing St John’s wort. Maximal enzyme induction is
generally not seen before two to three weeks but may then be sustained for at least four weeks after cessation of therapy with these medicines.

The Product Information for Implanon advises that women receiving short-term treatment with any of the above medicines or other hepatic enzyme inducing medicines should temporarily use a barrier method in addition to Implanon, i.e. during the time of concomitant medicine administration and for at least seven days after discontinuation. For women taking rifampicin, an additional barrier method should be used during the time of rifampicin administration and for 28 days after its discontinuation.

Prescribers are reminded that in women receiving long-term treatment with hepatic enzyme inducing medicines, the approved prescribing information recommends Implanon should be removed and another, nonhormonal, contraceptive method should be used.

3. Atypical antipsychotic agents and extrapyramidal side effects

It has been suggested that the atypical antipsychotic agents clozapine, risperidone, olanzapine, aripiprazole and quetiapine may have lower propensity for causing extrapyramidal side effects (EPS) when compared with older antipsychotic agents such as haloperidol, chlorpromazine and thioridazine. However, studies comparing the incidence of EPS between the older and newer agents are often confounded, especially by previous exposure to older agents.

ADRA data were searched for reports of EPS in association with the newer antipsychotic agents, using terms relating to nervous system disorders and movement disorders. The number of these reports, as well as total number of reports involving the medicine, is shown in the following Table. Reports for haloperidol are included for comparison.

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Total reports</th>
<th>EPS reports (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>147</td>
<td>33 (22.4)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>812</td>
<td>159 (19.6)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>315</td>
<td>42 (13.3)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1203</td>
<td>126 (10.5)</td>
</tr>
<tr>
<td>Clozapine</td>
<td>3775</td>
<td>70 (1.9)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>753</td>
<td>321 (42.6)</td>
</tr>
</tbody>
</table>

These data should be interpreted with caution. As with most data from spontaneous reporting, the data do not take into account factors influencing reporting rates, such as level of usage and intensive post-market safety monitoring programs. Reports with the newer agents are also likely to be confounded as described above, and ADRAC data for haloperidol are likely to be substantially more incomplete and limited than data for the newer agents. Therefore, the relative numbers of EPS reports shown in the Table do not necessarily reflect relative risk between these agents.

The ADRAC data suggest that, while the incidence of EPS may be lower with atypical antipsychotics than with the older agents, atypical antipsychotic agents are not devoid of EPS.

The most common reactions described in reports with the newer antipsychotic agents include dystonias, dyskinesias, akathisia and other non-specified EPS disorder. At the time of reporting, about one third of patients experiencing EPS had not recovered, with no distinction between medicines in this regard.

References:

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To subscribe, visit the Bulletin section of the TGA website at http://www.tga.gov.au/adr/aadrb.htm
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 front of the "Schedule of Pharmaceutical Benefits" and the "Australian Medicines Handbook", or from the Adverse Drug Reactions Unit ☏ 02-6232-8744, or from the website: 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 ) and clicking on “report problems” on the left.

For further information from the ADRAC Secretariat:
☎ 1800 044 114  Fax: 02-6232-8392  Email: adrac@health.gov.au

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

All correspondence to be addressed to: The Secretary, ADRAC, PO Box 100, Woden, ACT, 2606