COMMITTEE ON SAFETY OF MEDICINES

CURRENT PROBLEMS in Pharmacovigilance

MEDICINES CONTROL AGENCY

IN THIS ISSUE:

Now available via the internet at: http://www.open.gov.uk/mca/cuprblms.htm

Clozapine (Clozaril) and gastrointestinal obstruction

Early diagnosis and treatment are important

Clozapine (Clozaril) is an atypical antipsychotic used in patients with treatment resistant schizophrenia. The CSM/MCA have received 20 spontaneous reports associated with clozapine of serious adverse reactions resembling gastrointestinal obstruction. Seventeen of the reports were received in 1997/98, and three of these were fatal.

Reactions of this type are thought to be due to the anticholinergic properties of clozapine. It is therefore important to recognise that these types of reactions may be more likely to occur when clozapine is used in conjunction with other medications which have anticholinergic effects such as tricyclic antidepressants, anti-Parkinsonian agents, and other antipsychotics. In addition, particular care should be exercised in patients with a history of colonic disease or previous bowel surgery.

Prescribers are reminded of the importance of recognising and treating constipation in patients receiving clozapine to prevent the development of more serious complications. If possible, patients should be encouraged to adopt measures which may prevent constipation, such as a high fibre diet and physical activity.

Dose of CFC-free inhaled beclomethasone (Qvar▼)

Recommended total daily dose of Qvar▼ is lower than for CFC containing products

Chlorofluorocarbons (CFCs) damage the ozone layer and their use in metered dose inhalers (MDIs) will be phased out over the next few years. Qvar▼ (beclomethasone dipropionate (BDP)-HFA-134a) is the first CFC-free inhaled corticosteroid to be marketed in the UK.

Qvar▼ is only licensed for the prophylactic management of mild, moderate or severe asthma in adults. The specific formulation of BDP in HFA-134a results in smaller BDP particles and greater lung deposition when compared withCFC-BDP. Studies have shown that the increased lung delivery results in a 2-2.5 fold greater potency of Qvar▼ when compared with CFC-BDP. The use of high doses of inhaled corticosteroids has been associated with systemic adverse effects[1]. Therefore, it is important that patients being switched from CFC-BDP to Qvar▼are commenced on the appropriate equivalent dose.

If patients on budesonide inhalers are to be transferred to Qvar▼, the same instructions as described for CFC-BDP products should be followed. If transferring patients on fluticasone inhalers, the same total daily dose, up to a maximum of 800 µg/day should be substituted.

Switching patients to Qvar▼ from CFC-BDP involves two steps:

Step 1 : Determine the dose of CFC-BDP appropriate to the patient's current condition.

Step 2 : Convert the CFC-BDP dose to the Qvar▼ dose according to the table below:

Total Daily Dose (micrograms/day)				
CFC-BDP	200-250	300	400-500	600-750
Qvar	100	150	250	300

Total Daily Dose (micrograms/day)				
CFC-BDP	800-1000	1100	1200-1500	1600-2000
Qvar	400	500	600	800

Once transferred to Qvar▼ the dose should be adjusted to meet the needs of the individual patient. However, to avoid systemic adverse effects, **the minimum dose should be used at which asthma control is maintained.**

In patients not previously treated with an inhaled corticosteroid, Qvar▼ may be started at doses of between 100 µg/day and 800 µg/day in two divided doses according to the severity of the asthma.

Patients should be instructed in the proper use of their inhaler, including rinsing out their mouth with water after use. Patients should be advised that Qvar▼ may have a different taste and feel than a CFC inhaler.

Prescribers should remain vigilant to the risk of systemic adverse effects, particularly with prolonged, high dose therapy with inhaled corticosteroids including CFC-free products.

Please report all suspected adverse drug reactions to Qvar▼.

1. CSM/MCA *Current Problems in Pharmacovigilance* 1998;24:8.

Suppression of aldosterone secretion by heparin

Clinically significant hyperkalemia may occur rarely

Therapeutic doses of both unfractionated and low molecular weight heparins can inhibit the secretion of aldosterone[1]. This causes an increase in plasma potassium which may be clinically significant[2]. Certain types of patients seem to be more susceptible to the suppression of aldosterone secretion, such as those with diabetes mellitus, chronic renal failure, pre-existing acidosis, raised plasma potassium or those taking potassium sparing drugs. The risk appears to increase with duration of therapy. Plasma potassium should be measured in patients at risk before starting heparin and monitored regularly thereafter, particularly if heparin is to be continued for more than 7 days.

Product information for heparin products is being updated to reflect this new advice.

1. Oster JR et al. Am.J.Med.1995; 98: 575-586.
2. Monreal M et al. Eur.J.Clin.Pharmacol.1989; 37: 415-418.

Bezoar formation with sulcralfate (Antepsin)

Intensive care patients are at risk

Sucralfate, a complex of aluminium hydroxide and sulphated sucrose, is used in the treatment of duodenal and gastric ulcer and chronic gastritis. The suspension formulation (Antepsin Suspension) is also used in the prophylaxis of gastrointestinal haemorrhage from stress ulceration in seriously ill patients.

There have been seven reports world-wide of bezoar (an insoluble mass formed within the gastric lumen) associated with sucralfate use in intensive care patients, including premature infants. In addition, a publication from a French study in new born infants who received sucralfate revealed that 73% developed severe digestive problems and 36% presented with an occlusive syndrome requiring medical treatment[1].

Doctors should be aware of the risks of bezoar formation and potential intestinal obstruction with sucralfate in seriously ill patients, especially those receiving concomitant enteral feeds or who have predisposing conditions such as delayed gastric emptying. Sucralfate is not recommended for premature infants.

1. Le Boudec S. Arch.Pediatr.1996; 3 (Suppl 1): 111.

IN FOCUS..

In focus articles are a regular feature reviewing the adverse reaction profiles of selected newly introduced drugs. The reviews are based on the first 1-2 years of post-marketing experience. They should not be regarded as a comprehensive profile of safety.

Donepezil (Aricept▼)

Introduction

Donepezil (Aricept▼) is a selective inhibitor of acetylcholinesterase. It was licensed in 1997 for the symptomatic treatment of mild to moderately severe Alzheimer's dementia. It is recommended that treatment should be initiated and supervised by a physician experienced in the diagnosis and management of Alzheimer's dementia and should only be started if a carer is available who will regularly monitor drug intake.

Key safety issues

Due to its pharmacological properties, donepezil has the potential to produce certain undesirable effects. It may cause *bladder outflow obstruction* and should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. Patients at increased risk of gastric or duodenal ulcers should be monitored for symptoms.

Donepezil may cause *bradycardia* which could be hazardous to patients with sick sinus syndrome or other cardiac conduction conditions such as sinoatrial or atrioventricular (AV) block. *Syncope, bradycardia, sinoatrial block* and *AV block* are described in the product information. To date, the CSM/MCA have received 4 UK reports of heart block: one patient with first degree block, two with second degree block and one with complete heart block. However, there have been reports from abroad of complete heart block, cases suggesting Stokes-Adams syndrome and of several patients requiring cardiac pacing. In some cases it is difficult to attribute these events to donepezil, in view of the patients' age and pre-existing cardiac disease.

The CSM/MCA have received 20 UK reports of *seizure* in patients treated with donepezil. Although seizures might be ascribed to the underlying neurological condition in some cases, product information is being updated to include clearer warnings.

It is important to consider underlying drug-induced heart block in any patient presenting with syncope or a seizure who is taking donepezil, although these may occur without heart block as a precipitating factor.

The CSM/MCA have received several reports of psychiatric disturbances including *hallucinations, agitation*, and *aggressive behaviour* and these reactions have been added to the donepezil product information. There have been reports from other countries of *increased liver transaminases*, and rarely *hepatitis*, which is also being added to product information.

Other adverse reactions

Other adverse reactions to donepezil include *headache, diarrhoea, nausea, vomiting and other gastrointestinal disturbances, muscle cramps, fatigue, insomnia, dizziness and minor increases in blood levels of muscle creatine kinase.*

Drug interactions

Donepezil, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia. It should not be used concomitantly with drugs that have anticholinergic effects (e.g. hyoscine, benzhexol, benztropine, orphenadrine, procyclidine, tricyclic antidepressants), or with drugs that have cholinergic properties, such as other anticholinesterases (e.g. neostigmine, pyridostigmine).

There is the potential for a synergistic activity with beta-blocking agents leading to an increased risk of cardiac conduction defects. Ketoconazole, itraconazole, erythromycin and other inhibitors of cytochrome P450 3A4 may inhibit the metabolism of donepezil, leading to increased blood concentrations. In a study in healthy volunteers, ketoconazole increased mean donepezil concentrations by about 30%. Quinidine, fluoxetine and other cytochrome P450 2D6 inhibitors may also inhibit the metabolism of donepezil. In contrast, enzyme inducers, such as rifampicin, phenytoin, carbamazepine and alcohol may reduce blood levels of donepezil.

Conclusions

The safety profile of donepezil remains under close review, and doctors and pharmacists are reminded to report any adverse reactions which are suspected of being caused by donepezil.

For further information about the safe use of donepezil, please refer to the authorised product information.

Reporting of suspected adverse drug reactions by hospital pharmacists: the first year

Results from the first year are encouraging

In April 1997, the Yellow Card Scheme was extended to include hospital pharmacists as recognised reporters of suspected adverse drug reactions (ADRs)[1]; the reports submitted during the following 12 months have been evaluated, in order to determine the impact of hospital pharmacists on the Scheme.

Between April 1997 and March 1998, approximately 4% of reports received via the Yellow Card Scheme were submitted directly by hospital pharmacists. The extension of the Scheme to hospital pharmacists did not result in a reduction in the proportion of reports submitted by hospital doctors.

Although hospital pharmacists submitted a higher proportion of serious reports, they reported a lower proportion of reactions to new ('black triangle') drugs compared with hospital doctors. These findings mirror those of the pilot scheme for hospital pharmacist reporting[2].

Overall, we are encouraged that reports from hospital pharmacists are additional to those received from hospital doctors. However, there was variability in the number of reports received from hospital pharmacists across the UK and a low level of reporting of reactions associated with black triangle drugs. The MCA and CSM are currently examining ways of raising the profile of the Yellow Card Scheme, including hospital pharmacist reporting.

We are very grateful to pharmacists, as well as doctors for their continued support of the Yellow Card Scheme which is invaluable in protecting patients from unexpected drug safety hazards.

The full results of this analysis have been published in the Pharmaceutical Journal[3].

1. CSM/MCA Current Problems in Pharmacovigilance 1997; 23: 3.
2. Lee A. et al. BMJ 1997; 315: 519.
3. Davis S. et al. Pharm. J. 1999; 262: 366.

Advice about adverse drug reaction reporting

Through the Yellow Card Scheme

New medicines

Report ALL suspected reactions, that is, any adverse or unexpected effect, however minor, which could conceivably be attributed to the medicine. Please report even if the reaction is well recognised or if you are unsure of the causal relationship.

New medicines have an inverted black triangle▼ in the British National Formulary, MIMS and the ABPI Compendium of Data Sheets and Summaries of Product Characteristics.

Established medicines

Report SERIOUS suspected reactions, including those which are fatal, life-threatening, disabling, incapacitating, or which result in prolonged hospitalisation.

Do report a serious reaction even if it is already well recognised. There is no need to report minor reactions for established medicines.

Finding out about drug safety

Enclosed is an article outlining how drug safety information is made available to health professionals and patients. The article also provides details on how to request information about drug safety from the CSM/MCA.

Current Problems in Pharmacovigilance is produced by the Committee on Safety of Medicines and the Medicines Control Agency.

Editorial Board: Prof. A.M. Breckenridge, Prof. M. Kendall, Dr J. Raine, Dr E. H. Lee, Dr P. C. Waller, Dr P. Arlett, Dr M. Caldwell, Dr C. Hepburn.

Enquiries, comments and suggestions to Dr C. Hepburn, Medicines Control Agency, Market Towers, 1, Nine Elms Lane, London SW8 5NQ.

Doctors and dentists should notify a change of address by writing to Medical Mailing Company, PO Box 60, Loughborough, LE11 0WP, or by dialling the hotline number 0800 626387. Addresses supplied in connection with mailings on behalf of CSM and MCA will not be used for other mailings without the permission of the doctor concerned. **Pharmacists in Great Britain and Northern Ireland** do not need to communicate a change of address provided that this has already been notified to the Pharmaceutical Society with whom they are registered.