Domperidone: use in Parkinson’s Disease – consideration after the recent MHRA warning April 2014

Domperidone has been the anti-emetic of choice for Parkinson’s Disease (PD) patients with its use for this indication being off-label. Domperidone has the advantage over other antiemetics (eg metoclopramide and phenothiazines) of being less likely to cause central effects such as sedation and dystonic reactions because it does not readily cross the blood brain-barrier. For this reason it has been used in patients with PD to prevent nausea and vomiting both during treatment with apomorphine and also to treat nausea caused by other dopaminergic drugs.

Many of the available anti-emetics are contra-indicated in PD (BNF66):

- **Prochlorperazine (phenothiazine):** first-generation antipsychotic drug which acts predominantly by blocking dopamine receptors in the brain, side effects include extrapyramidal side-effects (parkinsonian symptoms including tremor, tardive dyskinesia) which can worsen the symptoms of PD
- **Metoclopramide:** dopamine antagonist causing extrapyramidal side effects (activity closely resembles that of phenothiazines) which can worsen the symptoms of PD
- **Cyclizine (antihistamine):** rare side-effects of antihistamines include extrapyramidal effects which can worsen the symptoms of PD

In April 2014 the MHRA issued a warning about domperidone: risk of cardiac side effects – restricted indication, new contraindications, and reduced dose and duration of use (embedded for information)

In summary the main points:

**Indication**
- Domperidone is now restricted to use in the relief of symptoms nausea and vomiting
- It should be used at the lowest effective dose for the shortest possible time

**Contraindications**
- Domperidone is contra-indicated in people:
  - with conditions where the cardiac conduction is, or could be, impaired
  - with underlying cardiac diseases such as congestive heart failure
  - receiving other medications known to prolong QT or potent CYP3A4 inhibitors
  - with severe hepatic impairment
- Patients with these conditions should have their treatment reviewed at their next routine appointment and be switched to an alternative treatment if required

**Duration of treatment**
- The maximum treatment duration should not exceed one week
- Patients currently receiving long-term treatment with domperidone should be reassessed at a routine appointment to advise on treatment continuation, dose change, or cessation

It should however be noted that ‘although the scope of the review does not cover use outside the licensed indications (off-label use) the principles behind these recommendations should be considered whenever domperidone is used’. Therefore although the review did not specifically consider the use of domperidone in PD patients it is clear from the review that the MHRA intend for the recommendations to be taken into account.
Additional points to note:

- The NICE CG on Parkinsons Disease: Diagnosis and management in primary and secondary care does not mention antiemetics (CG35, 2006) and no national guidance has been issued post the release of the MHRA warning on domperidone issued in April 2014.

- PD is a progressive movement disorder characterized by degeneration of dopaminergic neurones in the substantia nigra of the midbrain. Treatment is aimed at increasing dopaminergic stimulation of the striatal neurons involved in controlling movement, using dopamine-increasing agents or dopamine agonists. Concomitant stimulation of dopamine receptors results in the common side effects of nausea and vomiting.

- The BNF June 2014 (accessed online [link]) states that: ‘levodopa therapy should be initiated at a low dose and increased in small steps; the final dose should be as low as possible. Intervals between doses should be chosen to suit the needs of the individual patient. Nausea and vomiting with co-beneldopa or co-careldopa are rarely dose-limiting and domperidone can be useful in controlling these effects’

- Parkinson’s UK (accessed online [link]) recommends that: ‘In the early days of taking levodopa, you may feel sickness or nausea. But in most people this is mild and will pass as your body adjusts to the drug’

- The SPC for Madopar® (accessed online [link]) states that: ‘Undesirable gastrointestinal effects, which may occur mainly in the early stages of the treatment, can largely be controlled by taking Madopar with some food or liquid or by increasing the dose slowly’.

- Note that levodopa itself is contraindicated in some cardiac disorders eg severe cardiac arrhythmias and cardiac failure

- Antiemetics available more appropriate for use in those with PD include domperidone, cyclizine and ondansetron (Spencer, R. & Serumaga, B.(2011) Prescribing antiemetics for patients with Parkinson’s. Prescriber Vol 22 (18) pp 48-49)

Suggestions moving forward

1. All existing PD patients on long-term domperidone should be reassessed at their next routine appointment (some patients continued on long term domperidone for gut motility and not always on going nausea and vomiting):

- All PD patients with any of the above listed contraindications should have their domperidone stopped. A patient specific decision would need to be made as to whether an alternative antiemetic is required e.g. is the patient still experiencing on going nausea and vomiting. If an alternative antiemetic is required consider:
  - cyclizine (noting that antihistamines too can rarely cause palpitations & arrhythmias and can rarely cause extrapyramidal side effects that can worsen symptoms of PD) - advice received from King's neurology department June 2014
  - ondansetron noting that:
    - ondansetron is contraindicated for concomitant use with apomorphine based on reports of profound hypotension and loss of consciousness when used concomitantly
    - ondansetron should be used in caution in patients who have or may develop prolongation of QTc, including patients with electrolyte abnormalities, congestive heart failure, bradycardia and patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities as ondansetron prolongs the QT interval in a dose-dependent manner
- ondansetron is known to increase large bowel transit time and cause constipation
- ondansetron should be used in caution in hepatic impairment at a max 8mg daily in moderate or severe impairment
- ondansetron tablets are only licensed for use for a maximum of 5 days (post chemotherapy 8mg bd)
- June 2014 drug tariff price: 10 x 4mg tabs = £1.63 and 10 x 8mg tabs = £41.87 (note the orodispersible tabs are significantly more).

**Question re above options: limited choices. With ondansetron the contraindications / cautions are the same as for domperidone. Cyclizine – can worsen symptoms of PD. Both uses would also be off label.**

- All PD patients that do not have any of the above listed contraindications should have their need for continued domperidone reviewed. A patient specific decision would need to be made as to whether continued treatment with domperidone is required e.g. is the patient still experiencing ongoing nausea & vomiting. A decision about ongoing treatment with domperidone would need to made with the patient (or the patient’s carer) advising that the use of domperidone is outside the licensed indication and the recent MHRA review. If ongoing treatment is considered appropriate do not exceed dose of 10mg three times a day.

2. **New** PD patients starting PD medication that has nausea and vomiting as a common side effect:
   - Advise patients to take medication with food and do not automatically give an anti-emetic
   - If patient still experiences nausea and vomiting give advice that nausea and vomiting is usually transient and should ware off, therefore long term anti-emetic treatment not usually required. Give 1 months initial prescription for an anti-emetic
     - Consider using domperidone 10mg tds if not contra indicated (cardiac review prior to commencing therapy)
     - Consider cyclizine / ondansetron noting points above