LTHT Neurosciences CSU Consensus on the Use of Domperidone outside of MHRA restrictions

Indications for use outside of MHRA guidelines

- Patient’s with Parkinson’s disease (PD) may have poor gastrointestinal function and will have to take medications which cause nausea and vomiting, as expected adverse effects.
- Domperidone is the first line anti-emetic used in patients with PD as it does not cross the blood brain barrier and block dopamine receptors in the central nervous system.
- It is frequently used during initiation of treatment and continued management of nausea and vomiting, especially with apomorphine as this is highly emetogenic.
- The choice of anti-emetic is already extremely limited in PD patients, as standard anti-emetics are contra-indicated or have to be used with caution. For example:
  - anti-dopaminergic eg metoclopramide, levomepromazine, prochlorperazine
  - caution with anti-histamines eg. cyclizine
  - interact with medicines to manage PD. eg. ondansetron with apomorphine (ondansetron can be used with other PD medicines)

Risk Assessment and Monitoring

➢ Prior to prescribing domperidone, the LTHT Cardiology standard advice for prescribing QT prolonging medicines should be followed

➢ This includes an assessment of each individual’s potential benefit of treatment versus their risk factors and where possible avoidance of domperidone in those with the risk factors marked with an asterix below.

Patient risk factors which increase the risk of Torsades de Pointes with QT prolonging drugs include:

- Female
- >60 years old*
- Bradycardia*
- Concurrent use of more than one QT prolonging medicine*
- Concurrent use of potent CYP3A4 inhibitor* (specific to domperidone)
- Uncorrected electrolyte disturbances (hypokalaemia, hypomagnesaemia, hypocalcaemia)*
- Underlying heart disease such as heart failure, left ventricular hypertrophy and myocardial infarction*
- Congenital Long QT Syndrome*
- Severe hepatic impairment* (specific to domperidone)
Information on the potential for medicines to cause prolongation can be found in:
* manufacturer’s information (www.medicines.org.uk)
* the current BNF (www.medicinescomplete.com)
* Credible Meds (American resource) (www.crediblemeds.org)
* Stockley’s Drug Interactions (limited access via www.medicinescomplete.com)

If it is considered in the best interests of the patient to use domperidone, the information below can be used as a starting point to consider how to manage the patient appropriately.

No patient risk factors - treat, no monitoring

Patient risk factors present - treat, but monitor

Patient has pre-existing QT prolongation or congenital long QT syndrome - seek alternatives

Any patient who presents with palpitations, light headedness or dizziness whilst on domperidone should be offered an ECG, regardless of their risk factors

If monitoring is recommended, it is suggested to carry out a baseline ECG, repeated when drug levels are likely to be at steady state (1-2 weeks after starting domperidone).

Consider repeating the ECG after dose changes.

Be sure it is clear who is responsible for monitoring the ECG, and that they understand how to interpret any QT changes.

For background information:

* Normal QT intervals are <440ms for men and <460ms for women

* Changes of less than 5ms are generally considered to not increase the risk of arrhythmic events. Changes of between 5 and 20ms are usually also thought to be innocuous.

* In general, for every 10ms increase in the QT interval there is a 5% increase in the risk of arrhythmic events

* A change over baseline of >20ms should raise concern. A change of >60ms very significantly increases the risk of an arrhythmic event.

* Any change to over 500ms, regardless of the level over baseline, would also be a significant concern.
* If there is a significant change in a patient’s QT interval, check (and correct) any electrolyte imbalances. If this does not resolve the prolonged QT interval, consider a dose reduction or stopping the potentially causative medicine.

* Cardiology could be consulted if there is uncertainty about the ECG (e.g. persistent prolongation that is not resolved with the above measures) or in the presence of ventricular arrhythmia.

- The Association of British Neurologists (ABN) recommendations are listed below:

  Domperidone **SHOULD NOT** be prescribed routinely for patients commencing dopaminergic medication, and particularly for those over the age of 60 years or with serious underlying heart conditions such as congestive cardiac failure, severe hepatic impairment or significant electrolyte disturbance.

  **For Parkinson’s patients who develop nausea:**
  - Domperidone is the preferred anti-emetic.
  - A baseline ECG must be performed before prescribing domperidone, and the potential benefits / risks of prescribing domperidone discussed with the patient.
  - If the QTc is greater than 450 milliseconds in a male or more than 470 milliseconds in a female then domperidone should not be prescribed and a cardiology opinion obtained (ECG machines often overestimate, and less commonly underestimate). If a second QT prolonging drug or a strong CYP3A4 inhibitor is to be added then the ECG should be repeated (e.g., ketoconazole or erythromycin).
  - Patients should be advised to seek prompt medical attention if symptoms such as syncope or palpitations occur.
  - The prescription of domperidone should not routinely exceed 10mg tds for oral therapy, and should be used for as short a period as possible.
  - It is recommended that the initiation of apomorphine therapy be covered by domperidone at a dose of 20mg tds commencing 2 days before the first dose. The dose should be reduced to 10mg tds after 2 weeks if the patient is not experiencing nausea. If nausea persists or returns on reducing the dose, domperidone can be continued in the same dose.
  - The ECG should be repeated once at 2 weeks if the prescribed dose is maintained at more than 30mg daily.
  - Tolerance usually develops with oral therapy and can develop with apomorphine, so that a trial of domperidone dose reduction or withdrawal should be regularly considered.
  - Domperidone may also be beneficial in the management of orthostatic hypotension in Parkinson’s patients. The same recommendations will apply.
  - The initiation of domperidone should be under the recommendation and guidance of the Parkinson’s specialist.
  - For Parkinson’s patients who cannot swallow and need an antiemetic, rectal domperidone 30mg bd may be prescribed.
  - There is no need immediately to withdraw domperidone in any Parkinson’s patients currently on this drug. The continued necessity for prescribing domperidone should be reviewed at their next, and every subsequent, Parkinson’s clinic review.
When initiating apomorphine with domperidone, follow the recent MHRA Drug Safety Update Guidance:

Before starting treatment, carefully consider whether the benefits of concomitant apomorphine and domperidone treatment outweigh the small increased risk of cardiac side effects

- Discuss the benefits and risks of apomorphine with patients and carers and advise them to contact their doctor immediately if they develop palpitations or syncopal symptoms during treatment
- Check the QT-interval before starting domperidone, during the apomorphine initiation phase and if clinically indicated thereafter (eg if a QT-prolonging or interacting drug is started or if symptoms of cardiac side effects are reported)
- Regularly review domperidone treatment to ensure patients take the lowest effective dose for the shortest duration
- Advise patients to inform their doctor of any changes that could increase their risk of arrhythmia, such as:
  - symptoms of cardiac or hepatic disorders
  - conditions that could cause electrolyte disturbances (eg gastroenteritis or starting a diuretic)
  - starting any other medicines

- Please continue to report suspected side effects to apomorphine, domperidone, or any other medicine on a Yellow Card.

Patient information

Patients will be informed of the MHRA guidance and product licence. Patients receiving domperidone will be advised to seek medical attention immediately in the event of palpitations or fainting. Verbal consent should be obtained from the patient and documented in the patient notes

Communication with primary care

Letters to primary care will state that MHRA guidance has been taken into account, that risk assessment and patient counselling has taken place and that verbal consent has been obtained.

Authors

Dr Stuart Jamieson-Consultant Neurologist
Jeremy Robson-Advanced Clinical Pharmacist

Produced Dec 2016 and updated May 2017
Review date: May 2019
References

2. MHRA. Domperidone: risks of cardiac side effects May 2014
3. The Association of British Neurologists. Recommendations on the use of domperidone in Parkinson's Disease patients. Email communication (Forwarded by Dr Butterworth, Consultant Neurologist)
4. MHRA. Domperidone with apomorphine-minimising the risk of cardiac side effects. April 2016.