GUIDELINES FOR THE TREATMENT OF PARKINSON'S WITH APOMORPHINE (APO-go®)

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Abbreviations

BP-Blood Pressure
ECG – Electrocardiogram
ESR – Erythrocyte Sedimentation Rate
FBC – Full Blood count
GP – General Practitioner
MHRA – Medicines and Healthcare Products Regulatory Agency
PNS –Parkinson's Nurse Specialist
SC - Subcutaneous
UPDRS - Unified Parkinson's Disease Rating Scale
U&Es – Urea and Electrolytes

Background Information

Rationale for Use

Parkinson's is a common neurodegenerative disorder with the main motor symptoms of bradykinesia, rigidity and tremor. Motor fluctuations are a common complication of drug treatment and can have a high impact on the quality of life both for the person with Parkinson's and their carer. Apomorphine is a potent injectable dopamine agonist and an effective therapy for patients with Parkinson's who experience disabling motor fluctuations which persist despite individually titrated treatment with levodopa and / or other dopamine agonists.

Eligible Prescribers

Initiation of apomorphine therapy should be by a consultant neurologist or a hospital consultant with a specialist interest in Parkinson's.

Eligible Patients

Patients diagnosed with idiopathic Parkinson's with disabling motor fluctuations who are inadequately controlled by levodopa and / or oral dopamine agonists. The patient's treatment with levodopa, with or without dopamine agonists, should be optimised before starting treatment with apomorphine therapy. Patients selected for intermittent subcutaneous injections of apomorphine should be able to recognise the onset of their "off" symptoms and be capable of injecting themselves or else have a responsible carer to inject for them when required.

Product Information

Preparations

Apomorphine ampoules for injection or infusion (APO-go®) containing apomorphine hydrochloride **10mg/ml.** Ampoules are available as 1ml (10mg), 2ml (20mg) or 5ml (50mg).

Apomorphine pen for injection (APO-go® pen) a disposable multiple dosage injector system containing apomorphine hydrochloride. **10mg/ml**. Each pen contains 3ml (30mg).

Apomorphine pre-filled syringes for infusion (APO-go® PFS) containing apomorphine hydrochloride **5mg/ml.** Each pre-filled syringe contains 10mls (50mg).

Dosage

The daily dose of apomorphine varies widely between patients and can range from a few milligrams a day by intermittent subcutaneous injection to a maximum daily dose of 100mg per day. Individual bolus injections should not exceed 10mg. Continuous infusions start at 1mg per hour and are increased according to response usually up to 4mg per hour. Occasionally some patients require higher doses. Infusions should run for waking hours only and tolerance to the therapy does not seem to occur as long as there is an overnight period without treatment of at least 4 hours.

Administration

Apomorphine solution is administered by either subcutaneous injection or a continuous subcutaneous infusion using a small portable pump.

Adverse Effects

Very Common (≥1 in 10)

Hallucinations

Injection site reactions particularly with continuous use which may include subcutaneous nodules, induration, erythema, tenderness and panniculitis (inflammatory bumps/nodules). Other local reactions may also occur such as irritation, itching, bruising and pain.

Common (≥ 1 in 100 to <1 in 10)

Nausea and vomiting.

Transient sedation may occur with each dose of apomorphine hydrochloride at the start of therapy usually resolving over the first few weeks.

Apomorphine is associated with somnolence.

Yawning

Neuropsychiatric disturbances are common in parkinsonian patients. Apomorphine should be used with special caution in these patients. Transient mild confusion and visual hallucinations have occurred during apomorphine therapy.

For uncommon (≥ 1 in 1000 to <1 in 100 and rare ≥ 1 in 10000 to <1 in 1000 adverse effects, contra-indications, special warnings and interactions with other medicinal products please consult the appropriate Summary of Product Characteristics (SPC[1-3])

Instructions for Use/Handling

The solution should be inspected visually prior to use. Do not use if the solution has turned green. Apomorphine in any formulation should NOT be mixed with other medicinal products. Take care not to spill any apomorphine to prevent green stains on fabrics or surfaces. The immediate use of lemon juice can be of some use to avoid permanent stains.

Initiation of Apomorphine

Prior to Start of Treatment

1. Patient consent to the apomorphine challenge should be obtained by the prescriber and documented in the medical notes.
2. The patient / carer should be given information regarding apomorphine and the proposed treatment plan (Britannia have a patient pack available).
3. Baseline blood tests – U&Es/FBC/ESR/Coombs Test, BP (Lying and standing) and ECG

   A pre-treatment ECG is to exclude cardiac conduction problem or significant cardiac disease. Additional ECGs should be performed during the treatment initiation phase and as clinically indicated thereafter if the patient is prescribed domperidone (see point 5 below).
4. Base line motor scale of Unified Parkinson's Disease Rating Scale (UPDRS).
5. Domperidone should be given at a dose of 10mg three times daily at least two days prior to the apomorphine challenge.

   In 2014 and 2016 the MHRA[4,5] issued Drug Safety Updates relating to the use of Domperidone and Apomorphine due to a small increased risk of serious cardiac adverse effects. Updated contraindications include conditions with impaired cardiac induction, underlying cardiac disease, patients receiving other medication known to prolong the QT interval or potent CYP450 3A4 inhibitors, patients with significant electrolyte disturbances and those with moderate to severe hepatic impairment.

   If high risk consider cyclizine as an alternative antiemetic to Domperidone (ondansetron can compound hypotension when given with Apomorphine and is not advised).

6. Parkinson medication should be stopped six hours prior to the challenge so the patient is in an “off state” i.e. overnight for a morning challenge but must continue to have domperidone.
7. The initiation of apomorphine is usually carried out as a day case in a Day Hospital setting but there may be some instances where the patient may require to be admitted to a ward where staff are familiar with apomorphine and are trained in the use of the APO-go® pump.
8. The pharmacy department should be notified as soon as possible for any patient in whom apomorphine is planned to ensure supplies are available on the ward.

APOMORPHINE CHALLENGE

The Apomorphine challenge is necessary:

- To determine whether the patient has a positive response to apomorphine.
- To determine the threshold dose
- To observe the patient for adverse effects such as postural hypotension, nausea and hallucinations.

A challenge is positive if there is:

1. A decrease in the motor score of the UPDRS by at least 20%.

2. At least a 20% improvement in either timed hand tests (count finger taps) or timed walking.

Challenge Details

1. Administer 1mg apomorphine subcutaneously and observe patient's motor response for up to 30 minutes, monitor for side effects. Postural BP (lying and standing) should be monitored throughout.

2. If no response or an inadequate response is obtained a second dose of 2mg apomorphine hydrochloride is injected subcutaneously and the patient observed for an adequate response for a further 30 minutes. The dosage may be increased by incremental injections with at least a 40 minute interval between succeeding injections until a satisfactory response is obtained. If 7mg is administered without a positive effect the patient is usually considered to be a non responder. However in rare cases the medical team may consider administering a slightly higher dose (maximum 10mg).

3. On conclusion of the test re-introduce the anti-parkinsonian medications as per prescription at the next appropriate administration time. Once treatment has been established domperidone therapy may be gradually reduced in some patients but successfully eliminated only in a few, without any vomiting or hypotension.

   Once the appropriate dose is determined a single SC injection may be given at the first sign of an "off" episode or some patients will transfer directly onto the continuous infusion.

Ongoing Monitoring for Apomorphine Patients

6 Monthly U&Es/FBC/ESR/Coombs Test, BP (Lying and standing) and ECG (if remaining on domperidone). If Coombs test positive frequent FBCs required and may need to refer to haematologist.

Intermittent Subcutaneous Injection of Apomorphine

If the patient is appropriate for SC Injections once the appropriate dose is determined a single subcutaneous injection may be given into the lower abdomen or outer thigh at the first signs of an “off” episode. The patient should then be observed for the next hour to assess quality of response to treatment as absorption may differ with different injection sites. The optimal dose varies between individuals but once established remains relatively constant for each patient. It is recommended that the total daily dose of apomorphine hydrochloride should not exceed 100mg and the individual bolus injections should not exceed 10mg. It is important to remember to rotate injection sites to minimise nodule formation.

There are currently two ways to administer intermittent apomorphine:

1. Apomorphine solution drawn up in an insulin type syringe. This method needs to be prepared on a daily basis and unused syringes discarded after 24 hours. Drawn up syringes filled with apomorphine should be stored in the fridge when not being used immediately

2. Via a pre-filled pen injector system (APO-go®) with a “dial up” dose. Discard each pen no later than 48 hours from first use and the needle should be changed after each injection. Pen needles recommended for use with insulin pens are compatible with the APO-go® Pen. (Pen needles not more than 12.7mm in length and not finer than 30G).

The decision for either way of administration should be made after considering individual circumstances.

Continuous Subcutaneous Infusion of Apomorphine

Continuous Apomorphine infusion can be used in patients whose control remains unsatisfactory using intermittent injections and in those requiring many or frequent injections (> 10/day). Some patients may transfer directly onto the continuous subcutaneous infusion of apomorphine after the challenge test if felt not appropriate for intermittent injections.
Continuous infusion is started at 1mg/hr then increased according to individual response. Increases in infusion rate should not exceed 0.5mg/hr at intervals of not less than 4 hours. Patients are encouraged to be independent with the administration of the infusion, however not all patients and their carers are able to take on this responsibility. In these cases appropriately trained nursing staff (within hospital settings) or district nurses (within the community setting) will be responsible on a daily basis.

Presentation

Apomorphine solution for continuous infusion is available as **50mg/10mls** in a pre-filled syringe (5mg/ml) (APO-go® PFS). This presentation is pre-diluted with 0.9% sodium chloride. These syringes are available from the hospital pharmacy departments or via GP 10 prescription from the patient's General Practitioner and dispensed by the community pharmacist.

Infusion Pump and Accessories

The infusion pump used is called the APO-go® Pump and is available on loan from Britannia Pharmaceuticals. Britannia also provide free of charge the APO-go® pump

spacer, syringe pack containing dedicated 20ml chrono syringes and connectors, a preparation tray and towel.

The recommended infusion sets (Neria™ Guard) and large sharp boxes should be prescribed by GPs on a GP 10 prescription.

Site of Infusion
The best site for needle placement is the anterior abdominal wall below the umbilicus. Alternative sites are the upper outer aspects of the thighs, arms or shoulders. It is important to rotate the injection site daily to minimise possible localised skin irritation and to prevent formation of nodules at subcutaneous sites of injection. Nodules can be prevented by massaging the area with a barrier cream which will help to disperse any apomorphine contained within the subcutaneous tissue when the line is removed.

Training
Staff training for the APO-go® infusion pump and APO-go® therapy will be provided either by the Parkinson's Nurse Specialists (PNS) or a representative from Britannia Pharmaceuticals. The calibration and setting up of a continuous apomorphine infusion should only be undertaken by staff who have received the approved training on the APO-go® pump. The PNS will be responsible for the co-ordination of the training. The Apo-go® nurse advisor also can provide on the ward training.

The Threshold dose for Continuous Infusion of Apomorphine
Continuous infusion is started at a rate of 1mg per hour apomorphine hydrochloride then increased accordingly to individual response each day. Increases in the infusion rate should not exceed 0.5mg/hour at intervals of not less than four hours. Infusions should run for waking hours only. The infusion site should be changed every 12 hours. It is recommended that the total daily dose should NOT exceed 100mg.

Note
Apomorphine must NOT be withdrawn abruptly once the regimen is established. This will result in a deterioration of the patient's clinical condition leading to a lack of mobility, possible speech and swallowing problems, possible breathing problems and in rare situations neuroleptic malignant syndrome can develop indicating a medical emergency.

Admission of Existing Apomorphine Patients to Hospital.
If a patient receiving apomorphine is admitted to a ward where staff are familiar with the drug apomorphine and the APO-go® pump then the patient should remain on this pump. If dosing information cannot be obtained via the patient and/or carer, the district nurse (where relevant) responsible for setting up the patient's pump should be contacted. Pre-filled syringes of apomorphine 50mg/10ml are used with the APO-go® pump.

If a patient receiving apomorphine is admitted to a ward where staff are NOT familiar with the drug and the APO-go® pump then this pump should NOT be used and instead the apomorphine should be administered via the Agilia pump following details below. Note that if the patient is admitted during the day when the apomorphine infusion is being administered via the APO-go® pump the patient should continue with their apomorphine infusion via the APO-go® pump for the remainder of that day. Arrangements should then

be made to change the infusion device the next day to the device normally used in that ward which is usually the Agilia pump.

The PNS should also be informed as soon as possible after admission to ensure continuity of care for the patient. Other people who require to be informed of an admission of a patient on apomorphine include the relevant hospital pharmacy department (to ensure adequate supplies of apomorphine are available), the patient's general practitioner, community pharmacist and district nursing team (where relevant).

Transfer of Existing Patients on apomorphine via the APO-go® pump to the Agilia Pump

Only the apomorphine ampoules **50mg/5ml** should be used to prepare the subcutaneous infusion and must be DILUTED prior to use. It is prepared by using a 50:50 dilution of apomorphine and sodium chloride for injection 0.9%.

Procedure

Use two **50mg/5ml** apomorphine ampoules (NOT pre-filled syringes) and dilute with 10mls Sodium Chloride 0.9% to produce a final volume of 20mls and a final concentration of 100mg/20mls (5mg/ml). Prepare in a 50ml syringe.

The infusion should then be administered as follows:

mg of Apomorphine per Hour	Flow Rate of Diluted Solution (ml/hr)
1.0	0.2
1.5	0.3
2.0	0.4
2.5	0.5
3.0	0.6
3.5	0.7
4.0	0.8
4.5	0.9
5.0	1.0
5.5	1.1
6.0	1.2
6.5	1.3
7.0	1.4

Planning For Discharge

Patients requiring apomorphine hydrochloride treatment on discharge from hospital **require early identification** to ensure adequate primary care staff training. The PNS will ensure that the patient and/or a carer and/or district nurse team (where relevant) have a record of the prescribed drug therapy including hourly dose of apomorphine and the setting on their APO-go® pump.

Prior to discharge patients who have been transferred to the Agilia pump will transfer back to the APO-go® pump on day of discharge. This will be carried out by the PNS.

Roles within Co-ordinated Care

Specialists Role (Consultant/PNS)

- Confirm diagnosis of idiopathic Parkinson's
- Optimise anti-parkinsonian therapy
- Confirm patient's suitability for apomorphine therapy and the GPs agreement to prescribe apomorphine and carry out the ongoing monitoring tests
- Provide patient and carer support and advice in preparation for apomorphine therapy
- Liaise with Britannia Pharmaceuticals regarding training of patient/carer (where appropriate) and staff.
- Arrange pre-treatment with antiemetic domperidone or cyclizine and arrange for the temporary stopping of the anti-parkinsonian medication prior to the apomorphine challenge test.
- Apomorphine challenge test
- Monitor clinical response to apomorphine and conversion to intermittent subcutaneous injections or to continuous subcutaneous infusions where appropriate.
- Establish maintenance apomorphine dose prior to discharge
- Follow up assessment
- Liaise with pharmacy staff as soon as is practically possible for existing apomorphine patients being admitted to hospital and those patients in whom initiation of therapy is planned.
- Liaise with the district nurse team if relevant including when existing patients are admitted to hospital and when planning for discharge for both new and existing patients.

Hospital Pharmacist

- Liaise with consultant and nursing staff.
- Liaise with the appropriate community pharmacist for existing patients to ensure they are made aware of the hospital admission
- Liaise with the appropriate community pharmacist prior to discharge to ensure holding of apomorphine pre-filled syringes 50mg/10ml and holding of ongoing supplies of accessories provided by Britannia Pharmaceuticals.
- Ensure a supply of pre-filled apomorphine syringes 50mg/10ml is given on discharge from hospital.

Britannia Pharmaceuticals

- Loan of infusion pump and accessories (excluding infusion lines)
- An APO-go® helpline is available for patients and healthcare professionals 24/7, 365 days a year: 08448801327
- Training support for infusion pump and APO-go® therapy.

Appendix

1. APO-go® AMPOULES 10mg/ml Solution for Injection or Infusion (Apomorphine) Summary of Product Characteristics (Last updated on eMC on 03/07/2018). Available from www.emc.medicines.org.uk (accessed 23/02/2020)
2. APO-go® Pen 10mg/ml Solution for Injection (Apomorphine) Summary of Product Characteristics (Last updated on eMC on 30/01/2020. Available from www.emc.medicines.org.uk (accessed 23/02/2020)
3. APO-go® PFS 5mg/ml Solution for Infusion in Pre-filled Syringe (Apomorphine) Summary of Product Characteristics (Last updated on eMC on 03/07/2018). Available from www.emc.medicines.org.uk (accessed 23/02/2020)
4. Domperidone: risk of cardiac side effects. Indication restricted to nausea and vomiting, new contra-indications and reduced dose and duration of use. Drug Safety Update Vol 7 issue 10, May 2014:A1. Available from: https://www.gov.uk/drug-safety-update/domperidone-risks-of-cardiac-side-effects (accessed 23/02/20)
5. Apomorphine with domperidone: minimising risk of cardiac side effects. Drug Safety Update Vol 9 issue 9 April 2016: 5. Available from: https://www.gov.uk/drug-safety-update/apomorphine-with-domperidone-minimising-risk-of-cardiac-side-effects (accessed 23/02/20).