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Parkinson's disease

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Key points

- Parkinson's disease (PD) is associated with additional perioperative morbidity and mortality.
- Abrupt withdrawal or omission of anti-parkinsonian medication can have serious consequences.
- The transdermal dopamine agonist rotigotine is especially useful in nil-by-mouth patients.
- Many drugs used routinely in the perioperative period are contraindicated in patients with PD.
- Postoperative delirium is particularly common in PD, and is best managed by non-pharmacological methods.

Idiopathic Parkinson's disease (PD) is a common neurodegenerative disorder, affecting over 100 000 people in the UK. Patients with PD are undergoing increasingly complex surgical procedures, both elective and emergency. Perioperative management poses specific challenges to the anaesthetist, not only because the multi-system nature of PD increases perioperative mortality and morbidity, but also because of the difficulties of adequately maintaining anti-parkinsonian medication during the perioperative period.

Pathophysiology, diagnosis, and clinical features

The pathophysiology of PD is a loss of dopaminergic neurones in the pars compacta region of the substantia nigra, leading to the classical motor symptoms of parkinsonism: bradykinesia, muscle rigidity, and asymmetric resting tremor. There is considerable dopaminergic neuronal reserve—symptoms are often not seen until around 60–80% of dopaminergic neurones have degenerated. While the precise mechanism responsible for this cell death is unknown, age is the single most consistent risk factor. Patients with PD are therefore typically older and, as patients may live with PD for 20 yr or more, the prevalence in those aged over 65 is ~1%.

There is no specific diagnostic test for PD—the diagnosis is essentially clinical, using the UK Parkinson's Society Brain Bank Criteria,[1] although brain imaging may be useful to exclude structural lesions or to demonstrate features supportive of other neurodegenerative disorders. A number of other rarer neurodegenerative conditions (e.g. multiple system atrophy, progressive supranuclear palsy) also present with parkinsonism, and are collectively referred to as 'Parkinson-plus' syndromes.

It would be wrong to think of PD as simply a disorder of the extrapyramidal nervous system—it is a multi-system neurological disorder which causes disabling motor, neuropsychiatric, and autonomic dysfunction. While many of the clinical features of PD are present at diagnosis, some develop years later as the number of dopaminergic neurones continues to decrease (Table 1). Cognitive impairment is common (but not ubiquitous) as the condition progresses, with patients meeting criteria for PD dementia on average 11 yr after diagnosis.[2]

Pharmacological management

There are no established disease-modifying or neuroprotective therapies for PD. Pharmacological management is therefore oriented towards managing the symptoms of PD, to enable the patient to pursue as normal a lifestyle as possible. As the disease

Table 1 Clinical features of PD

Clinical features	Timing
Primary motor features	
Resting tremor (usually asymmetrical)	Usually at diagnosis
Bradykinesia	
Rigidity	
Early non-motor features	
Fatigue	May precede diagnosis
Depression/anxiety	
Sleep disturbance	
Constipation	
Later features	
Motor	
Gait change: stooped posture, shuffling gait with small steps, loss of arm-swing	5–10 yr after onset of symptoms
Dysphagia	
Expressionless face	
Small handwriting	
Soft speech	
Postural instability, leading to frequent falls	
Neuropsychiatric	
Cognitive disturbance: slowed cognitive speed, inattention, poor problem solving	Increasing likelihood as time from diagnosis increases
Dementia	>80% at 20 yr after diagnosis
Autonomic	
Postural hypotension	5–10 yr after onset of symptoms
Sialorrhoea (drooling or excessive salivation)	
Urinary dysfunction	
Sexual dysfunction	

progresses, it can be challenging to minimize the disability caused by PD against the troublesome side-effects of anti-parkinsonian drugs. For this reason, many PD patients have highly refined and complex drug regimes consisting of three or more different medications taken at different times throughout the day.

As the predominant pathophysiology of PD is a lack of dopamine in the substantia nigra, it would make sense to give exogenous dopamine replacement. However, dopamine cannot pass through the blood–brain barrier (BBB)—there is no cell membrane dopamine transport protein, and dopamine is too polar to diffuse across. Instead, the dopamine precursor levodopa is given, which crosses the BBB unaltered and is converted to dopamine within the central nervous system (CNS) by the enzyme dopa decarboxylase. This enzyme is also found within the peripheral nervous system—levodopa must be administered with a peripherally acting (i.e. does not cross the BBB) dopa decarboxylase inhibitor (DDI) to prevent peripheral dopaminergic side-effects such as tachycardia, arrhythmias, nausea, and vomiting.

A number of drug classes are available for the treatment of PD[3] (Table 2). Most anti-parkinsonian drugs increase the activation of CNS dopamine receptors, either by increasing dopamine concentration or by acting as dopamine receptor agonists. Levodopa remains the most effective treatment of motor symptoms in PD, but the side-effects become increasingly troublesome as the duration of treatment increases. For this reason, especially in early-onset PD, dopamine agonists may be used as initial therapy, and other drugs [monoamine oxidase type B inhibitors (MAOBIs), catechol-O-methyltransferase inhibitor (COMTIs)] are often used in combination with levodopa-DDI as 'levodopa-sparing' adjuvants.

Motor fluctuations

An 'on' period refers to a phase of relatively good symptom control. An 'off' period refers to poor symptom control, which may be

Table 2 Common pharmacological management of PD

Drug	Indication	Side-effects	Anaesthetic relevance
Dopamine agonist—acts at dopamine receptors, mimics the effect of dopamine			
Pramipexole, ropinirole	Monotherapy in early and established PD, adjunct to levodopa-DDI regime	Nausea, orthostatic hypotension, impulsive control disorders, somnolence	Risk of DAWS on acute withdrawal
Rotigotine	'Bridging' therapy in patients who are unable to take or absorb anti-parkinsonian medication, adjuncts to levodopa-DDI regime		Parenteral transdermal preparation
Apomorphine		Nausea, dyskinesias, cognitive impairment, postural instability	Subcutaneous infusion or injectable 'pen' for patients with troubling motor fluctuations, very emetogenic, risk of severe hypotension
Dopamine precursors—levodopa converted to dopamine in CNS. Peripherally acting DDI prevents peripheral conversion of levodopa			
Levodopa-carbidopa, levodopa-benserazide	Motor symptoms in established PD	Nausea, orthostatic hypotension, dyskinesia, hallucinations	Risk of PHS on acute withdrawal; short half-life (1.5 h)—need to continue enteral administration in prolonged procedures
Monoamine oxidase B inhibitors (MAOBIs)—prevents breakdown of dopamine by MAOB			
Selegiline, rasagiline	Used as monotherapy in early PD, or as adjunct to levodopa-DDI regime	Headache, arthralgia, exacerbation of levodopa side-effects when used as adjunct	Risk of serotonin syndrome (fever, hypertension, tachycardia, agitation) with meperidine
Catechol-O-methyl transferase inhibitors (COMTIs)—prevents breakdown of dopamine by COMT			
Entacapone Tolcapone	Adjunct to levodopa-DDI regime	Dark-coloured urine, exacerbation of levodopa side-effects	Reduce dose of other drugs metabolized by COMT pathways, for example, epinephrine

experienced a few hours after dosing when the dopaminergic medication is 'wearing off'. Choreiform dyskinesia is experienced by some patients (typically those having taken long-term levodopa therapy) 1–2 h after doses of dopaminergic medication ('peak dose dyskinesia'). These choreiform movements can be very disabling, and it is often difficult to find a balance between 'on' and 'off' periods: increasing the dose of dopaminergic medication to treat 'off' periods can worsen the dyskinetic periods. Instead, the dose of dopaminergic medication may be divided further, or the dose of the dopaminergic drug may be reduced and an MAOBI or COMTI added.

Withdrawal complications

Abrupt withdrawal of usual medication, as may occur in the perioperative period or during critical illness, can result in:

- parkinsonism-hyperpyrexia syndrome (PHS), due to withdrawal of levodopa. Symptoms mimic those of neuroleptic malignant syndrome: muscle rigidity, fever, cardiovascular instability, altered mental status (agitation, delirium, coma). PHS carries a significant mortality, up to 20% in untreated cases.
- dopamine agonist withdrawal syndrome (DAWS). Symptoms include: anxiety, nausea, depression, pain, and orthostatic hypotension. Withdrawal of dopamine agonists should be planned electively and simultaneously replaced with levodopa-DDI regimes.

Perioperative management

There is increasing evidence that PD is associated with an increase in perioperative mortality[4] and morbidity, including falls,[5] aspiration pneumonia,[4] venous thromboembolism,[6] and respiratory failure,[7] and also an increased postoperative length of stay.[4] Postoperative delirium is a particularly challenging problem, with studies identifying rates as high as 60%; the onset is often delayed.[8] With the complexity and frequency of many PD drug regimes, the perioperative management of dopaminergic medication may be challenging, even for patients undergoing relatively minor procedures. The consequences of missing medication doses or inadequate absorption of administered medication vary between patients: many experience the 'off' motor symptoms of freezing and rigidity, with consequences such as falls, swallowing difficulties, rigidity of voluntary respiratory muscles, poor cough, and failure to clear oral secretions. Even worse, the abrupt withdrawal of usual anti-parkinsonian medication may precipitate PHS or DAWS.

Preoperative assessment

When a PD patient is listed for elective surgery, the hospital's preoperative assessment service should be informed as soon as possible to allow comprehensive anaesthetic assessment, optimization by PD physicians, discussion of perioperative risk, and to plan perioperative dopaminergic drug management. The patient should be warned of the potential for less-than-optimal PD symptom control during the perioperative period. PD nurse specialists play a crucial role in co-ordinating preoperative management plans, in particular prophylactic strategies to prevent postoperative delirium. In addition to undertaking a routine history and physical examination, specific body systems require special focus in PD (Table 3). Additionally, most patients with PD are older and are therefore likely to have co-morbid disease which needs to be thoroughly assessed and optimized.

Table 3 Areas of focus in the anaesthetic assessment of a PD patient

System	Anaesthetic relevance
Airway	– Upper airway dysfunction (due to laryngeal/pharyngeal muscle dyskinesia) contributes to retained secretions, atelectasis, aspiration, post-extubation laryngospasm – Fixed flexion deformity of neck, which may impair laryngoscopic view
Respiratory	– Restrictive pulmonary deficit, due to rigidity, bradykinesia, or dyskinesia of respiratory muscles – Obstructive sleep apnoea common
Cardiovascular	– Cardiac arrhythmias – Orthostatic or exercise-induced hypotension, which may be due to PD or anti-parkinsonian drugs, increased risk of intraoperative hypotension
CNS	– Greater risk of postoperative delirium and hallucinations
Gastrointestinal	– Dysphagia, which contributes to aspiration pneumonia and malnutrition – Sialorrhoea (drooling) is a sign of advanced PD, but is thought to be a motor symptom (which impairs swallowing), rather than an excess of salivation. May need a drying agent before operation, for example, glycopyrrolate. Antimuscarinic (e.g. neostigmine) drugs increase the viscosity of saliva, thus further impairing swallowing – Increased prevalence of gastroesophageal reflux – Postoperative ileus or delayed gastric emptying may result in reduced absorption of enteral anti-parkinsonian drugs
Urological	– Increased risk of postoperative urinary tract infection

When PD patients present for emergency surgery, there is little time for optimization. In addition, those with intra-abdominal pathology will likely be made nil-by-mouth or have reduced intestinal absorption. Abrupt withdrawal of dopaminergic medication can have disastrous consequences—hospitals should have agreed protocols for the pharmacological management of these patients, or the means by which to seek urgent advice from PD specialists.

Perioperative drug management

The guiding principle of the perioperative pharmacological management of PD patients is to maintain CNS dopamine receptor activation. In most cases, this can be achieved by continuing the patient's usual anti-parkinsonian drug regime into the perioperative period: allowing patients to take their drugs up until anaesthetic induction, that is, within the 'nil-by-mouth' period with a sip of water, utilizing anaesthetic techniques which enable a rapid return to oral intake, for example, central neuraxial block, or by administering drugs enterally via a nasogastric tube (NB for dispersible preparations only—due to the differing bioavailabilities, a 30% dose reduction is suggested if the patient usually takes modified-release preparation). PD patients should usually be placed first on the operating list, so that the timing of drug administration is predictable, the risk of cancellation is minimized, and to ensure optimal early postoperative disease management.

In emergency and/or abdominal surgery, an early decision must be made about whether enterally administered dopaminergic drugs can be continued, or whether the patient must be converted to parenteral medication. Unfortunately, most anti-parkinsonian drugs can only be administered enterally. There are two main parenteral drug options:

- *Subcutaneous apomorphine infusion*. Apomorphine is a highly potent dopamine agonist with a number of side-effects, and requires a high degree of planning. Dosing is difficult and should be overseen by a PD specialist: a preoperative apomorphine challenge is recommended to find a dose which treats parkinsonian symptoms without serious adverse effects, for example, profound hypotension. The perioperative apomorphine infusion is then commenced 24–48 h before surgery, and continued until the patient's usual PD drugs are re-established. Apomorphine is highly emetogenic: patients are routinely pre-treated with 3 days of domperidone before apomorphine challenge or therapeutic infusion, and throughout the duration of apomorphine therapy.
- *Transdermal rotigotine*. In recent years, rotigotine (a transdermal dopamine agonist) has significantly simplified this complex clinical problem. Compared with apomorphine, rotigotine patches are much easier to dose, with an improved side-effect profile. However, they may not be sufficiently potent to manage patients on higher-dose anti-parkinsonian drug regimes. Ideally, conversion from a patient's usual drugs should be overseen by a PD specialist, but if there is insufficient time, a number of simple algorithms[9] or online calculators (e.g. http://www.parkinsonscalculator.com) are available. Many units adopt the approach of decreasing the initial rotigotine dose for acutely unwell or frail patients due to the risk of delirium and other neuropsychiatric sequelae.

Table 4 Pharmacological contraindications and cautions in PD

Drug class (example)	Effect
Contraindicated	
Phenothiazines (prochlorperazine) Butyrophenones (droperidol) Benzamides (metoclopramide) Typical anti-psychotics (haloperidol)	All are dopamine antagonists, resulting in exacerbation of parkinsonian symptoms
Caution	
Centrally acting anticholinergics (atropine)	May precipitate central anticholinergic syndrome: confusion, somnolence, restlessness; glycopyrrolate is a safe peripherally acting alternative
Halothane	Sensitizes the heart to the action of catecholamines: may potentiate levodopa-induced arrhythmias
Meperidine	Interacts with selegiline (MAOBI) to precipitate serotonin syndrome
Direct-acting sympathomimetics in those taking MAOBIs	Exaggerated vasoconstrictor effects
Epinephrine, in those taking COMTIs	Exaggerated sympathetic response
Fentanyl, alfentanil	Large doses may result in muscle rigidity

Intraoperative anaesthetic considerations

A number of drugs commonly used in the perioperative period are contraindicated in PD, and more still should be used with caution (Table 4). Considerations for the anaesthetist are as follows:

- *Regional anaesthesia*. For suitable types of surgery, central neuraxial block offers many advantages (Table 5).
- *Monitoring*. A significant tremor may induce monitoring artifacts: the ECG trace may mimic atrial flutter or ventricular fibrillation, and it may be difficult to measure arterial pressure non-invasively. Excessive sweating due to autonomic dysfunction may result in poor ECG electrode contact.
- *Induction of anaesthesia*. Just as in the general population, propofol may cause dyskinetic movements in PD patients. But propofol is also an anti-emetic and temporarily suppresses the parkinsonian resting tremor, and is therefore probably the best choice of induction agent in most situations. Thiopental and ketamine have been used in PD patients without harm, despite theoretical risks of

Table 5 Advantages and disadvantages of regional *vs* general anaesthesia

Mode of anaesthesia	Advantages	Disadvantages
Central neuraxial block	Intraoperative monitoring of parkinsonian symptoms	Muscle rigidity may make positioning difficult
	Further oral medication may be given intraoperatively	May be technically challenging with severe resting tremor
	Earlier return to postoperative oral intake	Risk of hypotension, especially in those with autonomic dysfunction
	Reduced use of systemic opioids, which may otherwise decrease gastrointestinal absorption	Tremor will only be abolished in the areas with motor block—tremor elsewhere may hinder surgery and affect monitoring
	Neuromuscular blocking agents not required, so no need for anticholinergic reversal agents	
General anaesthesia	Tremor is eliminated	Postoperative nausea and vomiting may preclude adequate dosing of anti-parkinsonian medication
		General anaesthesia in combination with dysphagia and ineffective cough is more likely to result in postoperative pneumonia

exacerbation of parkinsonian symptoms and exaggerated sympathetic response, respectively. With the exception of halothane, which potentiates levodopa-induced arrhythmias, the volatile anaesthetic agents are safe. Whichever drug is used for induction of anaesthesia, it is important that it is used judiciously: perioperative hypotension can be difficult to manage, and is especially common in the presence of autonomic dysfunction or dehydration.

- *Neuromuscular block*. Neuromuscular blocking drugs are safe to use in PD. However, residual block in the immediate postoperative period can mask parkinsonian symptoms, and neostigmine should be used with caution due to its thickening action on airway secretions. Perhaps, the ideal agent is rocuronium, as it may be reversed by sugammadex.
- *Opioids*. Meperidine should not be used for PD patients who take selegiline, due to the risk of precipitating serotonin syndrome. While all strong opioids have been used safely in PD patients, some cases of rigidity following high doses have been published.
- *Airway management*. Sialorrhoea can complicate airway management, and may be reduced with glycopyrrolate. Intubation should be considered if dysphagia is suspected. There is an increased prevalence of gastroparesis and gastrooesophageal reflux disease in PD patients, which may necessitate rapid sequence induction. Laryngoscopy may be difficult in the presence of a fixed flexion deformity of the neck.
- *Anti-emetics*. A number of commonly used anti-emetics are contraindicated in PD, due to dopamine antagonist effects (Table 4). 5-HT_3 receptor antagonists, for example, ondansetron, and histamine H_1-receptor antagonists, for example, cyclizine, have fewer side-effects. Despite being a dopamine receptor antagonist, domperidone does not readily cross the BBB and so is safe to use in PD.
- *Surgical diathermy*. PD patients with an implanted deep brain stimulator (DBS) will occasionally present for surgery. Surgical diathermy is not contraindicated,[10] but can damage the DBS leads, or can cause suppression or reprogramming of the neurostimulator. If surgical diathermy is necessary, the neurostimulator device should be switched off immediately before induction of anaesthesia, and bipolar diathermy should be used. Post-operatively, the neurostimulator should be checked to confirm normal function.

Postoperative management

Consideration should be given to a critical care admission, especially in the presence of a poor cough or swallow, sleep apnoea, or autonomic dysfunction. An early decision should be made regarding the feasibility of using the oral route for dopaminergic medication, preferably before the patient has left the post-anaesthesia care unit (PACU). In the presence of significant postoperative nausea or vomiting, the enteral route should be considered unreliable and the patient's dopaminergic medication supplemented by transdermal rotigotine.

A clear postoperative analgesic plan should be made before the patient has left the PACU—tremor and muscle rigidity may limit the ability of a PD patient to operate a patient-controlled opioid analgesic device.

Delirium is ideally managed using both individualized measures agreed before operation and also by following local and national guidance.[11] Non-pharmacological means are highly preferable, such as reorientation (explaining where the patient is, the time of day, and your role) and providing a suitable care environment.[11] Where drug management is absolutely necessary, typical anti-psychotics such as haloperidol should never be used, due to their anti-dopaminergic effects; benzodiazepines such as lorazepam are considered safer in PD. Quetiapine is often considered in clinical practice for troubling symptoms of psychosis, although evidence is lacking.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

Podcasts

This article has an associated podcast which can be accessed at https://academic.oup.com/bjaed/pages/Podcasts.

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