Medication in the peri-operative period

In the first article in a series on peri-operative medication, Mohamed H. Rahman and Jane Beattie give a general overview of the concepts relating to this area of drug therapy, including guidance on which drugs should be continued and which considered for discontinuation.

According to Department of Health statistics, from April 2002 to March 2003, over 13 million operations were performed by the NHS in England alone. Procedures range from routine minor surgery, such as incision of a perianal abscess, to major surgery, such as pancreateoduodenectomy (Whipple’s procedure). The peri-operative period is the time between admission to hospital for surgery and discharge and “peri-operative medication” is a general term used to describe all medicines administered during this period. There is currently no national guidance on peri-operative drug therapy but the United Kingdom Clinical Pharmacists Association (UKCPA) intends to form a focus group to produce such guidelines. This article gives guidance only — each patient should be treated individually.

Medication history

When a patient is admitted for surgery, a key role for pharmacists is to take a medication history. Patients may be taking medicines regularly or on a “when required” basis and these can interact with drugs used during the peri-operative period or interfere with surgery. For example, selective serotonin reuptake inhibitors can interact with drugs such as pethidine and tramadol (which block presynaptic reuptake of serotonin), to precipitate “serotonin syndrome”. This is a potentially fatal condition due to overstimulation of the central nervous system, characterised by rigidity, shivering, confusion, coma, autonomic instability, nausea, diarrhoea, diaphoresis, flushing and, rarely, rhabdomyolysis.

It is essential to ensure that the anaesthetist and surgical team are aware of all medicines that the patient is — or has recently been — taking, including over-the-counter and herbal medicines. For example, it is important for the anaesthetist to know if patients are taking a tricyclic antidepressant (TCA) because they will be at an increased risk of developing hypotension or cardiac arrhythmias during anaesthesia. Stopping TCAs, however, is unnecessary if the anaesthetist is aware that their use is continuing because the choice of anaesthetic can be tailored to the individual’s need.

Nil by mouth

If anaesthesia is induced in patients with a full stomach there is a risk of regurgitation of stomach contents, followed by pulmonary aspiration (known as Mendelson’s syndrome).

Therefore, where possible, fluids and food are discontinued for two and six hours, respectively, before anaesthesia is induced. The ingestion of clear fluids two hours before surgery (as compared with nine hours) has not shown any significant differences in volume or acidity of gastric contents.

When reviewing a patient’s medication during the nil-by-mouth (NBM) period, the following issues need to be considered:

- How long is the patient expected to be NBM?
- What modifications are required to drug therapy in the NBM period?
- Which medicines must be continued and which must be stopped?
- Where medicines are continued, are suitable alternatives available if the usual route or formulation is inappropriate?
- Have alternative arrangements been made for medicines which must be continued, but which have no suitable formulations available?
- Is an unlicensed preparation required? (If it is, has the consultant accepted responsibility and have local procedures for unlicensed medicine use been followed?)
- Does the continuation of a medicine pose a risk because of interaction with an anaesthetic agent?

To avoid interrupting long-term therapies, oral medicines may be administered in the NBM period with small amounts (sips) of clear oral fluids. However, continuation may not be possible for all medicines — some have special requirements, for example, alendronate tablets must be taken with at least a tumbler of water (200ml) to avoid oesophageal reactions.

Pre-medication

Pre-medication usually refers to a single dose of a medicine given to a patient to relieve pre-operative anxiety (eg, diazepam 2–5mg). Both the volume and acidity of accidentally inhaled gastric contents influence the severity of lung damage in Mendelson’s syndrome and an H2-receptor antagonist or proton pump inhibitor is sometimes prescribed to increase stomach pH and reduce the volume of gastric fluid.

Discontinuing medication

The risks and benefits must be considered when deciding to continue or stop medication in the peri-operative period and, where possible, these should be discussed with the patient at a pre-operative clinic. The anaesthetist should be contacted if in any doubt. A comprehensive list of interactions can be found in specialist textbooks or by contacting local medicines information units. Where a drug is discontinued, the elimination half-life should be used to estimate the time required for the drug to be removed from the body.

Generally, medicines used to control life-threatening conditions should be continued. Stopping such medication can cause rebound exacerbation of the disease, delaying surgery or increasing the risk of post-operative complications. Withdrawal symptoms can also complicate matters. For example, stopping neuroleptic drugs can result in the rapid onset of extrapyramidal syndromes, nausea and restlessness.

It is essential to optimise the treatment of patients with chronic diseases so that they are in the best condition to cope with and recover from surgery. For example, beta-blockers, antimuscarinics and steroids must be continued in patients with asthma or chronic obstructive pulmonary disease. Nebulised drugs may be required. These patients may also need supplementary steroid doses immediately before or after surgery (see p289).

It may not always be possible for the patient to continue taking his or her medicine in the same way or form. For example, a patient who is unable to swallow may need to be given medicines via a feeding tube (see www.pjonline.com).
**Surgery increases adrenocorticotrophic hormone and cortisol levels**

Panel 1). Switching to a different drug altogether might also be required.

In an emergency, the adjustment of drug therapy before surgery is not always possible, for these patients it is essential to be aware of possible complications related to recently administered drugs, which otherwise would have been stopped or modified pre-operatively.

In general, few drugs need to be stopped before surgery.

**Hormone replacement therapy** Major surgery, (especially gynaecological, orthopaedic or vascular leg surgery), is a predisposing factor for venous thromboembolism (VTE). In women who take hormone replacement therapy (HRT), the risk of developing a peri-operative VTE is two to four times higher than in women who do not. Consideration should, therefore, be given to stopping HRT before surgery.

However, the Committee on Safety of Medicines has advised that there is no need for women without other predisposing risk factors for VTE to stop HRT. Risk factors include: personal history, family history of VTE in a first-degree relative aged under 45 years, obesity, trauma, long-term immobilisation and varicose veins. If HRT is continued, thromboprophylaxis with heparin (or low molecular weight heparin) and graduated compression hosiery is advised. In women who do have other predisposing risk factors the risks of continuing therapy may exceed the benefits and HRT should be discontinued four weeks before major elective surgery or surgery to the legs.

**Combined oral contraceptives** Combined oral contraceptives (COCs) have been reported to increase the risk of VTE. The risk is particularly high in women who have blood coagulation disorders, such as factor V Leiden mutation. It is not necessary to discontinue COCs for minor surgery or where a short period of anaesthesia is required (eg, removal of wisdom teeth), but consideration should be given to discontinuing all oestrogen-containing oral contraceptives (and alternative contraception used) four weeks before major elective surgery and all leg surgery. The manufacturer of Loestrin recommends discontinuation six weeks before surgery.

The risk of VTE versus the possibility of pregnancy must be discussed with the patient and the final decision must be jointly made by the doctor and the patient. If COCs are not stopped, thromboprophylaxis is strongly advised. Current evidence suggests that progesterone-only pills need not be discontinued in the perioperative period.

**Tamoxifen** Women receiving tamoxifen are also at a higher risk (two- to three-fold) of VTEs but there is clear evidence that the benefits for women being treated with tamoxifen for breast cancer outweigh the risks, and it is important that women taking the drug continue to do so. However, 40 per cent of VTEs in women taking tamoxifen occur within three months of surgery or immobility, so these patients should be made aware of the symptoms. Patients coming into hospital for major elective surgery (eg, secondary breast reconstruction) could have their tamoxifen stopped up to one month before surgery to minimise the risks, but this must be discussed with the oncology team. Omitting several doses peri-operatively should not affect long-term survival, but there is no evidence to prove or disprove this.

For patients taking tamoxifen to treat infertility, the manufacturers of Nolvadex recommend discontinuing medication at least six weeks before surgery.

**Methotrexate** During the peri-operative period, fluid restriction can lead to hypovolaemia and diminished renal function. Methotrexate is predominantly cleared from the body via the kidneys and after each drug administration.

### Panel 1: Feeding tubes

**Medication via feeding tubes** (eg, nasogastric, nasojejunal, percutaneous endoscopic gastrostomy, percutaneous endoscopic jejunostomy) generally falls outside a drug’s product licence. The prescriber must, therefore, accept liability for any adverse outcomes resulting from administration via this route.

**Suitability of formulation** Soluble tablets can be easily dissolove in a small volume of water but non-dispersible tablets should be avoided because sediments increase the risk of tube blockage. Uncoated and sugar-coated tablets can be crushed using a mortar and pestle, but other tablets must not be crushed. Crushing destroys the formulation properties of enteric-coated tablets, alters peak and trough levels of modified release tablets and alters absorption of sublingual tablets. Crushing antibiotic or cytotoxic tablets poses a risk to staff via inhalation. Some capsules can be opened and the contents diluted with a small amount of water, but the suitability of this must be checked with the manufacturer. In some cases, a different drug preparation may be used (eg, a shorter acting nitrate instead of a slow release preparation to avoid peaks and troughs). Where liquid preparations are used, they must be shaken well before administration. Viscous preparations may block tubes, and therefore need to be diluted with water before administration. Sterile water must be used for jejunal tubes because this route bypasses the acid barrier in the stomach. Liquids can be associated with osmotic diarrhoea (high osmolality and sorbitol content) and altered bioavailability. Additives in injections may make administration via tubes unsuitable. Tubes should be flushed with water before and after each drug administration.

**Site of delivery** Absorption may be unpredictable because the location of the tube may be beyond the main absorption site for the drug.

**Tube-specific interactions** Problems include:

- **Drug-feed interactions** For example, the vitamin K in feed means that doses of warfarin may need to be increased.
- **Feed can decreasing drug absorption** (eg, ciprofloxacin) In such cases the feed should be stopped one or two hours before and after the drug is given (depending on type of drug) and the tube must be flushed well.
- **Interactions causing tube blockage** For example, if acidic drugs are given with antacids precipitation can occur. Such contact should, therefore, be avoided and an alternative drug formulation found or the tube flushed well with water.
- **Some drugs (eg, phenytoin) binding to feeding tubes** The drug should be diluted with water and the tube flushed well.

Further guidance on the administration of drugs via feeding tubes is available at: www.bapen.org.uk
Sometimes, the type of surgical procedure will influence which drugs must be stopped. For example, metoclopramide is contraindicated after pyloroplasty or gut anastomosis because of its ability to stimulate gastrointestinal contractions. Similarly, antispasmodics must be avoided in patients undergoing surgery that may be associated with prolonged NBM periods, because of the increased risk of paralytic ileus.

Antiepileptic drugs are usually continued peri-operatively because abrupt withdrawal may precipitate rebound seizures. It is good practice to measure serum levels of antiepileptics before surgery to ensure therapeutically safe drug levels. The exception to continuing anticonvulsant agents is before neurosurgery to excise the epileptic focus. In this case, benzodiazepines may be useful to prevent any pre-operative seizures as serum concentrations of anticonvulsants fall below the therapeutic threshold.

Finally, it should be remembered that discontinuing some medicines may affect the efficacy or toxicity of others (e.g., if cimetidine is stopped plasma levels of anticoagulants, ciclosporin and theophylline will change).

### Lithium

Lithium prolongs the action of both depolarising and non-depolarising muscle relaxants. This alone is not a sufficient reason to discontinue lithium, but anaesthetists need to be aware of continued dosing. Some consultant teams recommend that lithium is discontinued at least 24 hours before major surgery, and resumed after the operation, when renal function and fluid and electrolyte balance (especially any hyponaetraemia) return to normal. Any discussion about discontinuation must involve the patient’s psychiatrist because abrupt cessation may precipitate a withdrawal syndrome. For minor surgery the normal dose can be continued because little metabolic disturbance is expected.

### Monoamine-oxidase inhibitors

Potentially fatal interactions can occur between monoamine-oxidase inhibitors (MAOIs) and many peri-operative drugs. For example, the use of pethidine or dextromethorphan in patients receiving MAOIs have been associated with excitatory reactions (due to excessive CNS serotoninergic activity) such as agitation, marked hypertension and haemodynamic instability, hyperpyrexia, flushing, seizures, coma and even death. CNS depression, such as hypotension and respiratory depression, has also been observed. The MAOI could be discontinued at least two weeks before the operation. However, the risk of psychiatric relapse must be considered. Another option would be to switch to a newer, reversible MAOI two weeks before surgery (e.g., moclobemide has an elimination half-life of two to four hours and can be withheld on the morning of surgery). The third and, probably, the best option, is to continue the MAOI but to use an anaesthetic technique avoiding any drugs known to interact with MAOIs.

- Those with known adrenal insufficiency (e.g., Addison’s disease)
- Those receiving long-term steroid therapy, especially at doses above 5mg prednisolone daily. Topical and inhaled steroids can be absorbed systemically and high dose inhaled steroids may also cause adrenal suppression

The exact dose of corticosteroid administered peri-operatively will vary depending upon previous steroid dose, duration of therapy, type of surgery and function of the hypothalamic–pituitary–adrenal axis. Doses of supplementary intravenous hydrocortisone range from 25mg to 100mg up to four times a day. Parenteral hydrocortisone is used until the patient is able to tolerate oral corticosteroid again. It is preferable (but not common practice) to administer hydrocortisone as an infusion (as opposed to bolus doses) to avoid large swings in plasma cortisol levels. Higher than required doses should be avoided because of impaired wound healing, risk of infection and delayed recovery. The BNF gives a dose equivalence chart for corticosteroids. It should be noted that this does not take account of mineralocorticoid effects, nor does it take account of variations in duration of action.

### Restarting medication after surgery

After surgery, oral medicines can be restarted at their pre-operative doses as soon as the patient is able to swallow small amounts of fluid. The drug can often be given sooner, by an alternative route, such as via rectal, transdermal, parenteral or nasogastric delivery, if a patient is likely to be NBM for a long time (e.g., due to post-operative nausea and vomiting or delayed gastric emptying).

Some patients require a temporary change to an alternative treatment regimen after surgery. Examples include administration of intravenous heparin before starting warfarin again, and short acting intravenous insulin, to a patient with Type 1 diabetes who normally uses twice daily subcutaneous insulin. Peri-operative drug therapy in people with cardiovascular disease or diabetes will be covered in the next articles in this series.

Some drugs should not be restarted immediately after surgery. For example, to minimise the risk of postoperative VTE, COCs should only be restarted at the first menses occurring at least two weeks after full mobilisation.

It should be remembered that some drugs may no longer be required after surgery. For example, aminosalicylates are discontinued following a total colectomy and alpha-adrenoceptor blocking drugs are stopped after a transurethral resection of the prostate gland. Conversely, surgery may necessitate the introduction of a new drug, for example, thyroxine following a total thyroidectomy. In addition, calcium supplementation may be required if parathyroid gland function is not preserved and alfalcacidol is also given to promote calcium absorption. Surgery may also necessitate the addition of drugs for peri-operative pain, nausea, vomiting and constipation.

### Further reading and information


### Topics in this series

Further articles in this series on peri-operative drug therapy will look at:
- Peri-operative drug therapy in patients with cardiovascular disease or diabetes
- Peri-operative venous thromboembolism
- Antibacterial prophylaxis
- Post-operative nausea, vomiting and pain