



October 2011

# circuit

clinical initiatives, research and current updates in treatment

## Postoperative Nausea & Vomiting

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### Introduction

Postoperative nausea and vomiting (PONV) are potential undesirable outcomes after anaesthesia or sedation.<sup>1</sup> Despite the armoury of antiemetics currently available, PONV remains a challenge in the management of surgical patients. It is reported to affect 20-30% of all patients after surgery. In high-risk patients, the incidence can be as high as 80%.<sup>1,2</sup> It has also been rated by patients as one of the least desirable outcomes after surgery. PONV results in prolonged recovery time, increased nursing care and costs, delayed hospital discharge and may lead to subsequent unplanned admissions.<sup>1,2</sup>

### Minimising Risk Factors for PONV

The risk factors for PONV vary greatly between patients (Table 1). Factors that have shown to independently predict PONV include female gender, non-smoker, history of motion sickness or PONV, duration of operation and opioid administration.<sup>2</sup> PONV has also been more frequently associated with certain types of surgery and the risks may vary dependent upon which pre-anaesthetic medications, anaesthetic drugs and postoperative analgesics are administered.<sup>1,2</sup>

Adjustment of a number of these risk factors may significantly decrease the incidence of PONV and increase postoperative patient satisfaction. Measures that are shown to be effective include the preferential use of regional over general anaesthesia in both children and adults. The risk for PONV has been shown to be nine times less among patients receiving regional anaesthesia than those using general anaesthesia.<sup>1</sup> When general anaesthesia is required, propofol is the drug of choice for the induction and maintenance of anaesthesia. Propofol significantly reduces incidence of PONV compared to volatile anaesthetics or nitrous oxide.<sup>1</sup> The combination of propofol and air/oxygen further reduces this risk.<sup>1</sup> Reducing intraoperative and postoperative opioid use can also help minimise PONV. Evidence suggests that non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors and, to a lesser degree, intraoperative ketamine, may potentially have an opioid-sparing effect post-operatively thus reducing the incidence of opioid-related nausea and vomiting.<sup>1,2</sup> If neostigmine is required for reversal of neuromuscular blockade, avoidance of high doses (> 2.5mg) is associated with reduced PONV.<sup>2</sup> Therefore, careful management of baseline risk factors play an important role in minimising PONV.

### Factors that increase the risk

Patient factors	<ul style="list-style-type: none"> <li>• Female gender</li> <li>• Non-smoker</li> <li>• History of motion sickness or PONV</li> <li>• Age &gt; 40 years old</li> </ul>
Surgical factors	<ul style="list-style-type: none"> <li>• Type of surgery (e.g. gynaecological, ENT, intra-abdominal, breast, plastic and neurosurgery)</li> <li>• Surgical technique (e.g. laparoscopic surgery)</li> <li>• Increased duration of surgery</li> </ul>
Anaesthetic or drug factors	<ul style="list-style-type: none"> <li>• Inhaled anaesthetics</li> <li>• Use of intraoperative or postoperative opioids</li> <li>• Neostigmine (Doses &gt; 2.5mg)</li> <li>• Inadequate postoperative hydration</li> </ul>

Table 1: Risk factors for PONV in adults<sup>1,2</sup>

### Drugs Used for Prophylaxis of PONV

The recommended pharmacological agents for prophylaxis of PONV in adults are listed in Table 2. The decision to use pharmacological intervention should be based on a valid assessment of the patient's individual risk for PONV.<sup>1,2</sup> Several models have been developed to identify those patients at sufficient risk of PONV to warrant antiemetic prophylaxis.<sup>1</sup> One such model is described in Table 3. However, a more liberal approach to utilisation of antiemetics is necessary for patients in whom vomiting poses a medical risk (e.g. wired jaw, increased intracranial pressure, gastro-oesophageal surgery) or where the patient or care provider has a strong preference to avoid PONV.<sup>1</sup>

A Safety Alert issued 15/9/11 by the US Food and Drug Administration (FDA) updates the risk for the rare but potentially fatal ventricular tachyarrhythmia, torsades de pointes (TdP), with the 5HT<sub>3</sub>-antagonist antiemetic, ondansetron (Zofran® and various generic brands), for further details: <http://www.fda.gov/Drugs/DrugSafety/ucm271913.htm>

cont >

Drugs	Dose and route	Recommended timing of administration
Dexamethasone	4-8mg IV	At induction
Dolasetron	12.5mg IV	End of surgery. Timing may not affect efficacy.
Droperidol	0.625mg-1.25mg IV	End of surgery
Granisetron	1mg IV	End of surgery
Prochlorperazine	6.25-12.5mg IM/IV	End of surgery
Promethazine	6.25-25mg IV	At induction
Ondansetron	4mg IV	End of surgery
Tropisetron	2mg IV	End of surgery

**Table 2: Commonly used Antiemetics and the recommended doses and timing for prevention of PONV in adults<sup>1,2,3</sup>**

It is now accepted that antiemetics acting on different pathways work independently and have cumulative benefits to any single antiemetic intervention.<sup>1,2</sup> 5-HT<sub>3</sub> antagonists (e.g. ondansetron, tropisetron) are most effective in both the prevention and treatment of PONV when given at the cessation of anaesthesia. The 5-HT<sub>3</sub> antagonists have a favourable side effect profile and the different agents in the class are considered comparable in most instances.<sup>1,2,3</sup> The corticosteroid dexamethasone is an effective antiemetic and is best given at the induction of anaesthesia rather than at the end of the surgery. It can also be effectively combined with 5-HT<sub>3</sub> antagonists for additive effect.<sup>1,2</sup> Droperidol is a neuroleptic agent that may be used in addition to 5-HT<sub>3</sub> antagonists. It is most effective when given at the end of surgery.<sup>1,2</sup> It may also be incorporated into a patient-controlled analgesia (PCA) to help reduce the risk of opioid-induced nausea and vomiting.<sup>1</sup> Unpleasant adverse effects of droperidol include restlessness and extrapyramidal symptoms. The doses of droperidol used for the management of PONV are relatively low and are unlikely to cause significant cardiovascular events, such as QT interval prolongation.<sup>1,2,3</sup> Promethazine has some benefits in the prevention and treatment of PONV although its sedative effects may delay emergence from anaesthesia.<sup>1</sup> At standard clinical doses (i.e. 10mg IV), metoclopramide has not been shown to have any relevant efficacy in the prevention of PONV.<sup>1,2</sup>

Risk factor	Action
None	Pharmacological intervention not required
Present:	Minimise anaesthesia-related risk factors, or consider regional anaesthesia
1-2 risk factors	<b>Monotherapy:</b> 5-HT <sub>3</sub> antagonist <b>OR</b> dexamethasone <b>OR</b> droperidol
3-4 risk factors	<b>Dual Therapy:</b> 5-HT <sub>3</sub> antagonist + dexamethasone <b>OR</b> 5-HT <sub>3</sub> antagonist + droperidol
>4 risk factors	Combination Therapy: 5-HT <sub>3</sub> antagonist + dexamethasone + droperidol + propofol (total IV anaesthesia)

**Table 3: Risk stratification model for utilisation of Prophylactic Antiemetics in PONV<sup>2</sup>**

Non-pharmacological PONV prophylactic measures that have been studied and demonstrate potential antiemetic efficacy include acupuncture and transcutaneous electrical nerve stimulation (TENS).<sup>1</sup>

An emerging area in the prevention and treatment of PONV is the possibility of individualising treatment based upon the genotype of the patient. It has been observed that population variations in the drug-metabolising enzyme CYP2D6 may dictate response to many of the 5-HT<sub>3</sub> antagonists, including ondansetron, tropisetron and dolasetron.<sup>4</sup> Patients who are classified as 'ultra-rapid metabolisers' clear these drugs at an accelerated rate – predisposing them to PONV. Whilst CYP2D6 genotyping is not currently routine in clinical practice, this may provide sound rationale for preferential utilisation of granisetron for PONV, as granisetron is not metabolised by CYP2D6.<sup>4</sup>

**Drugs Used for Treatment of Emergent or Refractory PONV**

If, despite adequate prophylaxis, patients develop PONV within 6 hours of returning from the post-anaesthesia care unit, treatment should be given with an antiemetic of a different pharmacological class to that used for prophylaxis.<sup>1</sup> There is no demonstrated benefit to repeating the dose/drug administered perioperatively within 6 hours.<sup>1</sup>

All available 5-HT<sub>3</sub> antagonists indicated for PONV are currently considered to be equally efficacious in the treatment of established vomiting, and are the only pharmacological class of antiemetics studied adequately in this setting.<sup>1</sup> Should patients experience ongoing PONV despite administration of a suitable rescue antiemetic, an alternative intravenous agent (e.g. dexamethasone, droperidol, promethazine) should be considered.

**Conclusion**

PONV prophylaxis should be considered for patients at a moderate to high risk of experiencing nausea and/or vomiting after surgery. Depending on the level of risk, patients may be initiated on monotherapy or combination prophylactic therapy. High-risk PONV patients should receive prophylaxis with combination antiemetic therapy or a multimodal approach that includes two or more interventions. As not all surgical patients benefit from pharmacological prophylaxis, it is important to identify patients who are at higher risk to help select the most cost-effective use of therapy.

References available upon request.

**Chemotherapy and Hair Loss: An Update from San Antonio and Overview of Current Evidence**

**William Chong, APHS Pharmacy Tennyson**

On December 8-12 2010, I had the opportunity to attend the 33rd Annual San Antonio Breast Cancer Symposium (SABCS). It was held at Henry B. Gonzalez Convention Centre, San Antonio, Texas, USA. SABCS is an international scientific symposium for interaction and exchange among scientists and clinicians working in breast cancer.

One of the presentations I attended was presented by Dr. Michelle Melisko, an Assistant Clinical Professor at the Helen Diller Family Comprehensive Cancer Centre, University of California, San Francisco (UCSF). Her topic for the talk was on emerging techniques to avoid hair loss during chemotherapy and focused on the various techniques of scalp cooling and ongoing trials at UCSF. This article will be based on the presentation given by Dr Melisko and aim to provide an overview on the various techniques used to avoid hair loss during chemotherapy.

Chemotherapy-induced temporary hair loss is one of the most common and distressing side effects of cancer therapy<sup>1</sup>. It impacts on a patient's decision to accept or decline chemotherapy and as high as 8% of patients may choose chemotherapy regimens with possibly less favourable treatment outcomes as long as these regimens do not cause severe hair loss<sup>2</sup>. Chemotherapy-induced hair loss is a constant reminder for patients of their treatment and has an impact on various

daily-life activities<sup>3</sup>. It can have a negative impact on body image, psychological well being and self esteem<sup>4</sup>. Chemotherapy-induced hair loss is a burden on about half of breast cancer patients with one study finding that some patients considered the loss of hair to be more difficult to cope with than the loss of their breast<sup>5</sup>. It has been suggested that the timely provision of a wig and appropriate patient preparation can reduce distress in a high number of patients.<sup>2</sup>

Since about 1970, attempts to prevent chemotherapy-induced hair loss have been made through the development of pharmacological and non-pharmacological measures such as mechanical strategies and scalp cooling. With the exception of folic acid and a liposomal alternative of conventional doxorubicin, up to now the results of many pharmacological agents under evaluation has been disappointing in the prevention of chemotherapy-induced hair loss<sup>6</sup>. Minoxidil is an agent that stimulates hair growth, but the results of topical application in animal models and chemotherapy patients has been very inconsistent<sup>7</sup>. A mechanical strategy such as a scalp tourniquet, has been designed to reduce blood flow to scalp hair follicles during peak cytostatic agent levels with intravenous chemotherapy. However, side effects such as nerve compression and headaches are reported with the use of a tourniquet and there are no recent reports of tourniquet use<sup>8</sup>. Currently, preventative measures mainly focus on scalp cooling.

Scalp cooling works by two main mechanisms. It works by inducing vasoconstriction and a reduction in metabolic rate. Vasoconstriction leads to reduced blood flow to the hair follicles during the period of peak plasma concentrations of the chemotherapy agent while reduced biochemical activity makes hair follicles less vulnerable to the damage of chemotherapy agents<sup>9</sup>.

Over the past few decades, scalp cooling has been practised with several methods, such as simple bags with crushed ice, frozen cryogel packs and packs with an endothermic cooling reaction. Examples of precooled caps are ChemoCap™, Elasto-Gel™ Cold Caps and Penguin Cold Caps. The use of precooled (frozen) caps requires frequent cap changes due to thawing, are labour-intensive for the nursing staff and can be very uncomfortable for patients due to the cap's heavy weight.

More recently, cooling systems have been adopted that cool continuously. These caps are cooled by chilled liquid or air and are more convenient for the nursing staff as no cap changes are needed. Cooling machines that use liquid circulation include Paxman (PSC-1 and 2, Orbis) and Dignitana (DigniCap™), while Amit Technology (SCSII™) uses chilled air. The few studies performed to examine which scalp cooling method is the most effective are inconclusive<sup>10</sup>.

Breed et al<sup>11</sup> gathered the results of 36 scalp cooling studies without controls and found the median value for good hair presentation in the studies was approximately 80%. One of the largest studies on scalp cooling is an observational non-randomised multi-centre study from the Netherlands. In this study, 1415 patients were recruited from 2006 until 2009 in 27 hospitals using the Paxman scalp cooling systems. They found that 50% of the patients with scalp cooling had good hair preservation.<sup>10</sup> Together, these studies show that there is clear evidence that scalp cooling can prevent chemotherapy-induced hair loss.

The success of scalp cooling depends on many factors such as the dosage and type of chemotherapy, the number of chemotherapy courses, the administration method, the temperature and scalp cooling times<sup>12</sup>. For example, when anthracyclines or taxanes were used, a positive effect has been demonstrated. However, if a combination of anthracyclines and taxanes were used, the results were considerably less positive.<sup>11</sup>

Scalp cooling is generally well tolerated. The most common reported side effects are headaches, unpleasant effects due to the heaviness of the cap and coldness, dizziness and transient light-headedness.<sup>10</sup> Headaches are mostly not severe and can usually be prevented by paracetamol. Scalp cooling is contraindicated in patients with cold sensitivity, cold agglutinin disease, cryoglobulinemia and cryofibrinogenemia and in patients with a tendency to develop migraines<sup>13</sup>. Scalp cooling should also not be used in patients with haematological malignancies or melanoma patients receiving adjuvant or curative chemotherapy.<sup>10</sup>

Scalp cooling has been rather controversial in the curative chemotherapy setting due to concerns centred around the risk of scalp metastases. In a review

from 2005, scalp skin metastases were found in nine patients out of a total of approximately 2500 patients in 56 scalp cooling studies and in all these cases, it was deemed very unlikely that the metastases were a result of scalp cooling.<sup>10</sup> Lemieux et al were the first who specifically designed a study, albeit retrospective to assess the incidence of scalp metastases in early breast cancer patients who received neoadjuvant or adjuvant chemotherapy. They studied 553 patients with scalp cooling and 87 without scalp cooling. With a median follow-up of more than 5 years, the incidence of scalp metastases was low in both groups, 1.1% in women who received scalp cooling and 1.2% without scalp cooling<sup>14</sup>.

In conclusion, scalp cooling is well tolerated and effective in the prevention of chemotherapy-induced hair-loss but is not suitable for all chemotherapy patients. Further research is needed to identify the determinants of success and to find out which scalp cooling method is the most effective.

Attendance at SABCS was made possible with support from APHS, GlaxoSmithKline, Merck Sharp & Dohme and Roche.

References available upon request.

## Oral bowel cleansing solutions: The best choice is not so clear

John Forster - APHS Pharmacy Hollywood

"77% of patients believe that bowel preparation is the most difficult part of a colonoscopy"<sup>2</sup>

### The need for a clear bowel

Colonoscopy and radiological investigations of the large intestine require that the bowel is cleared of faeces. This is to ensure that lesions are not missed, and that procedures are not cancelled because of poor mucosal visualisation caused by inadequate cleansing<sup>1</sup>. Such cleansing is usually attained by the administration of any of a variety of oral bowel cleansing solutions. Unfortunately, there is no clear evidence as to which is the best solution to use. Instead it is a matter of choosing a solution that is best for the individual patient.

### Oral bowel cleansing solutions used in Australia

In Australia, there exists a variety of products to achieve a clear bowel. The most common are sodium phosphate (NaPO<sub>4</sub>), polyethylene glycol (PEG), and the diphenylmethanes (bisacodyl, sodium picosulphate).

### Cleansing products

1. Sodium Phosphate – Fleet Phospho-Soda® solution, Diacol® tablets
2. Polyethylene glycol – ColonLYTELY®, Glycoprep®, Moviprep®
3. Diphenylmethanes – bisacodyl; sodium picosulfate - Picolax®, Picoprep®

Often a combination of these products is used to ensure a clear bowel is attained. Commercially available combination products include Go Kit® (bisacodyl/magnesium salt) and Prep Kit-C® (picosulfate/PEG)

### 1. Sodium Phosphate

Sodium Phosphate is an osmotic laxative which draws water into the intestinal lumen, resulting in peristalsis and bowel evacuation<sup>2</sup>. A 45mL dose of NaPO<sub>4</sub> can produce a significant 1.8L of fluid and stool loss.

Postural hypotension occurs in 16% of patients<sup>8</sup>. Other serious adverse effects include hypocalcaemia, hypokalaemia, hypernatraemia, hypovolaemia, hyperphosphataemia, ischaemic colitis and acute kidney disease<sup>2</sup>. However, the majority of these adverse effects occurred at higher or inappropriate dose levels, or where the patient was predisposed to an adverse effect<sup>1</sup>.

Safe bowel cleansing with NaPO<sub>4</sub> requires proper dosing and hydration, awareness of contraindications and precautions, adequate patient instruction, and patient compliance<sup>1</sup>. In recent years additional safety alerts have been issued regarding the potential for systemically absorbed NaPO<sub>4</sub> to cause acute phosphate nephropathy in certain patients: children and the elderly;

pre-existing renal impairment; active colitis; concurrent use of drugs affecting kidney perfusion, eg ACE inhibitors, Angiotensin 2 antagonists, diuretics, NSAIDs.<sup>9</sup> Furthermore, with an increasing incidence of chronic kidney disease (and an ageing population), the incidence of adverse effects due to NaPO<sub>4</sub> is likely to increase unless patients are carefully screened at the time of prescribing<sup>3</sup>.

Otherwise, in the absence of aforementioned risk factors, NaPO<sub>4</sub> represents a safe and effective bowel cleansing option<sup>1</sup>.

## 2. Polyethylene Glycol

Also known as Macrogol 3350, polyethylene glycol (PEG) is a high molecular weight carbohydrate that holds water in the bowel<sup>4</sup>. As it is ingested with large volume of water and balanced with electrolytes, there is less risk of dehydration and electrolyte disturbances than for NaPO<sub>4</sub>, with similar efficacy when administered appropriately<sup>3</sup>. However due to the large volume (3-4L) of unpalatable fluid that must be ingested, nausea, bloating, abdominal pain, and poor tolerability can result<sup>4</sup>. Patients not able to tolerate PEG often had a poorly cleansed colon as a result<sup>1</sup>. Moviprep® is a newer, higher concentration PEG product containing ascorbic acid, requiring only 2L of lavage solution (with 1L clear fluids in between) for comparable effect, with increased likelihood of patient tolerability.<sup>12</sup>

## 3. Diphenylmethanes (bisacodyl and sodium picosulfate)

Co-administered in combination products with osmotic laxatives (most commonly magnesium salts), these drugs work locally to stimulate peristalsis and promote water and electrolyte accumulation within the colon<sup>4</sup>.

The smaller volumes make them more attractive to patients than PEG; however adequate hydration must still be maintained to avoid dehydration and electrolyte disturbances.

Bisacodyl is administered in the form of a small tablet which is generally well tolerated.

Sodium picosulfate is better tolerated than NaPO<sub>4</sub> in terms of taste, nausea and vomiting<sup>3</sup> and produces similar cleansing results. These products are often favoured because of their ease of administration and high patient tolerability. However, these drugs are relatively contraindicated in the presence of renal impairment and cardiac failure<sup>4</sup>:

As is the case for sodium phosphate, sodium picosulfate can cause dehydration, hyponatraemia (which may cause altered consciousness and/or seizures), hypokalaemia (which can cause cardiac arrhythmias and metabolic alkalosis) and other electrolyte disturbances<sup>5</sup>. Infants, the elderly (>55 y), the frail, and patients with congestive heart failure and impaired renal function are at higher risk of these adverse effects<sup>6, 12</sup>.

### Tips for a successful procedure

- Confirm the date and time of the procedure
- A special low residue diet may commence 3 days prior to procedure
- Check contraindications
- Review and adjust medications if necessary (e.g. hypoglycaemics/insulins, diuretics, drugs that cause constipation such as opioids, critical drugs such as organ transplant rejection medicines that may have absorption affected during the lavage<sup>12</sup>)
- Specific directions regarding appropriate volume of hydration fluids to avoid dehydration or hyponatraemia due to excessive water consumption
- Drinking chilled, quickly and with a straw may reduce taste and improve compliance for unpalatable products i.e. PEG

### Key safety points

A superior oral bowel cleansing solution has not been identified. Therefore it is concluded that the safest approach is to minimise the risks associated with using bowel cleansing solutions. This can be achieved by<sup>6</sup>:

- 1) The clinician undertaking an assessment as to the safety of the intended preparation in each patient BEFORE prescribing.
- 2) Oral and written information being provided to the patient at the time of supply.

### Further Reading:

Detailed Consensus Guidelines by British medical specialist associations can be found at [http://www.rcr.ac.uk/docs/radiology/pdf/oral\\_bowel\\_cleansing\\_guidelines.pdf](http://www.rcr.ac.uk/docs/radiology/pdf/oral_bowel_cleansing_guidelines.pdf)

References available upon request.

## New Drug Brief: Palonosetron: Aloxi®

Ben Stevenson, APhS Pharmacy Tennyson

### Approved indication:

Palonosetron was registered by the Therapeutic Goods Administration (TGA) on 26 June 2006 for the prevention of nausea and vomiting induced by cytotoxic chemotherapy.

### Approved dosage:

Presentation: 250mcg/5mL solution for injection.

- Dose: Adults: 250 mcg single dose approx 30 min before chemotherapy.
- Administer by intravenous infusion over 30 seconds.
- Flush the infusion line with normal saline before and after administration.
- Repeated dosing within 7 days is not recommended.

### Efficacy and safety:

- Compared with older 5HT<sub>3</sub> antagonists, palonosetron has a higher binding affinity to the 5HT<sub>3</sub> receptors, a higher potency, a significantly longer half-life (40 hours, 4-10 times longer than that of dolasetron, granisetron or ondansetron) and an excellent safety profile<sup>3</sup>
- Two separate phase III studies have compared it to dolasetron (100mg IV) and ondansetron (32mg IV) in moderately emetogenic chemotherapy (MEC) and shown it to be significantly better in the acute and delayed phases of CINV<sup>3</sup>
- Two further phase III studies compared it (in combination with dexamethasone) against ondansetron (32mg IV) and granisetron (40mcg/kg IV) in highly emetogenic chemotherapy (HEC) and in both cases it was shown to be as effective in the acute phase but superior in the delayed phase<sup>3</sup>
- Palonosetron has also been studied in combination with aprepitant and dexamethasone and this was shown to be a highly effective regimen<sup>3</sup>
- Pharmacokinetic studies did not reveal any differences between young patients and those > 65 years of age and demonstrated dosage adjustment is not necessary for patients with renal or hepatic impairment<sup>3</sup>
- The most common side effects for palonosetron include those common with the class and include headache and constipation<sup>3</sup>

### Accessibility:

Palonosetron is listed on the Pharmaceutical Benefits Scheme as a Restricted benefit: Management of nausea and vomiting associated with cytotoxic chemotherapy being used to treat malignancy which occurs within 48 hours of chemotherapy administration.

References available upon request.

If you have any queries regarding Circuit content and authors please contact 07 3347 9500 and speak with one of the following editors, Ben Stevenson, Chris Giles, Scott McGregor or Stacy LaHood.

Every effort has been made to ensure this newsletter is free from error or omission