

# PONV: What is the role of the Anesthesiologist

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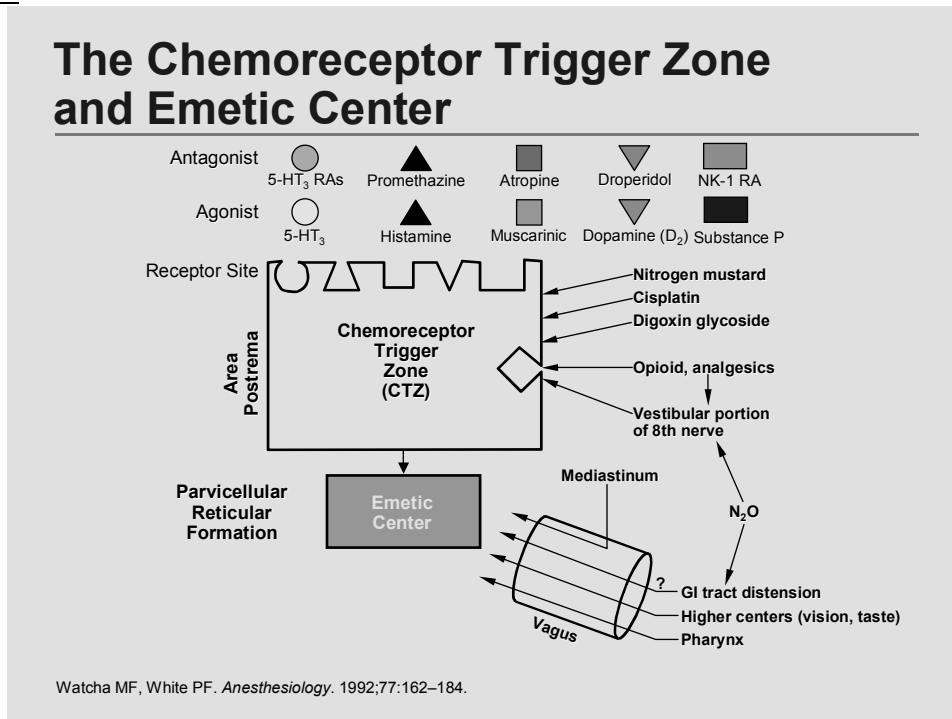
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In an editorial in 1997 in *Anesthesiology* Dennis Fisher called post-operative nausea and vomiting (PONV) the "Big Little Problem". [1]. Why is this? The occurrence of PONV although associated with limited morbidity is amongst the primary concerns of patients following anesthesia and surgery.[2-4]. Thus it is important that we have an understanding of the problem and from this develop management guidelines. This presentation will discuss; the patho-physiology of PONV, the drugs used for its prevention and treatment, present controversies, and guidelines for PONV.

## Patho-physiology of PONV

Nausea and vomiting is generated via 2 centers in the brain (figure 1). These are the chemoreceptor trigger zone (CTZ) and the emesis center. The CTZ has 5 different receptors that may activate it (and similarly provides 5 different sites for anti-emetics to act). The multiple number of receptor sites involved in PONV also open therapeutic approaches to multi-modal therapy. This will be discussed in more detail below. The CTZ sits in the area postrema where it is readily in contact with emetogenic chemicals in the blood stream. The emesis center in the reticular formation is connected to the CTZ via neuronal pathways. The emesis center itself may be activated via stimuli (e.g. gastric distension through the vagus nerve). [5]

Figure 1



The incidence of PONV has been reviewed by several authors.[6-11] The incidence is dependant on a variety of factors related to the patient, the procedure and the anesthetic. The overall incidence varies from 22-38%.

## Factors Impacting the Incidence of PONV

Patient factors include age (young > old), gender (female > male), obesity, an history of PONV or motion sickness, delayed gastric emptying and preoperative anxiety.[7, 12]. A history of smoking is associated with a decreased incidence of PONV.

Procedure factors are the type of surgery and increasing duration. Surgical procedures associated with a higher incidence include strabismus surgery, intra-abdominal or laparoscopic surgery, ear nose and throat procedures, plastic and gynecological surgery.[12].

The role of anesthetic factors in the etiology of PONV are multiple and controversial. The use of pre-medication to allay anxiety has been advocated to reduce PONV. In the out patient setting this seems to play less of a role and pre-medication is generally reserved where anxiety is a significant concern for the patient. Gastric distension has also been implicated in increasing the incidence of PONV. This has led many to the habit of inserting a naso-gastric tube as a routine to deflate the stomach and drain any gastric contents. This practice is not without morbidity and the proof that it diminishes PONV is meager at best. [13] Anesthetic technique does play a significant role on the incidence of PONV. Regional anesthetic techniques have been considered to result in a lower incidence of PONV. In an excellent review of the incidence of PONV in regional anesthesia by Alan Borgeat et al they agree that the overall incidence is likely to be lower however this is not invariably so and will vary by surgery, regional technique used and a multitude of other factors.[14]. Propofol is now well recognized as an anti-emetic and has been associated with a decreased incidence of PONV when used as the induction agent for brief procedures (< 60 Minutes) or as part of a Total Intravenous Anesthetic.[15] The volatile anesthetics are associated with a similar increase in the incidence of PONV in the first 2 hours post-operatively. They have much less impact on PONV occurring after 2 hours. There also appears to be a dose response relationship with the use of volatile anesthetics on PONV. [16]. Lack of adequate hydration is associated with an increased incidence of PONV and supplemental pre-operative fluid loading (15 ml/kg) has been shown to reduce PONV.[17] The use of opiate analgesics in increasing the incidence of PONV is controversial. Opiates are clearly emetogenic, but so is pain and thus the clinician tries to strike a balance. In the post-operative period opiates are clearly the most potent causes of PONV. The duration of surgery and the use of neuromuscular blocker antagonists are also implicated in increasing PONV.

Apfel et al recently conducted a very large study to determine a simple model to predict the incidence of PONV. The model determined that gender (female), history of PONV or motion sickness, non-smoking status and the use of post-operative opiates were the 4 most significant factors in predicting the incidence of PONV. If none, one, two, three, or four of these risk factors were present, the incidences of PONV increased from 10%, to 21%, to 39%, to 61% and to 79% respectively.

## Drugs used in the Prevention and Treatment of PONV

Eighteen drugs have been considered to be useful in the treatment or prevention of PONV. The evidence for the efficacy of each individual drug is highly variable. [18]

### 5-HT<sub>3</sub> Receptor Antagonists

This is the newest and presently the most common class of drugs used for PONV. The initial success of ondansetron for both PONV and chemotherapy induced nausea and vomiting has prompted the development of numerous others within the same class. These include dolasetron, granisetron and tropisetron. Although there are several studies comparing their efficacy, probably at truly equipotent doses they are very similar. They vary primarily by their duration of action. At present ondansetron retains the major market share worldwide and is also the most studied. There have been several very large studies and meta-analysis evaluating the efficacy of ondansetron. These studies tend to indicate that the optimal dose for prophylaxis is 4 mg with possible 8 mg for high risk patients.[19, 20] In a study of over 2000 high risk patients 4 mg of ondansetron resulted in no PONV in 62% of patients compared to 42% in patients receiving a placebo.[21] This decreases to 29% for the 24 hour post operative period. The calculated number needed to treat to prevent PONV with ondansetron is approximately 5, in patients who are at risk for PONV, compared with placebo. Ondansetron has an effective duration of 4-6 hours whereas granisetron has a duration of about 12-14 hours. It has become apparent that PONV is significant for several days post surgery and thus the importance of longer lasting 5 HT<sub>3</sub> receptor antagonists or repeat dosing methods has become evident. As ondansetron is short lasting an oral disintegrating tablet has been developed for its use following discharge home.[22] The most common side effect of the 5 HT<sub>3</sub> receptor antagonists are sedation (14%), headache (17%), dizziness (9%) and anxiety (2%).[21]

### Steroids

Over the past few years dexamethasone has become one of the primary anti-emetics for PONV. This is largely because of its low cost and lack of side effects. When administered alone at doses of 8-10 mg I.V. the number needed to treat to prevent an episode of PONV was 4 (and 7 when using appropriate doses in children). When combining dexamethasone with a 5 HT<sub>3</sub> receptor antagonist the number needed to treat to prevent an additional episode of PONV compared to the 5 HT<sub>3</sub> receptor antagonist alone is 7.[23] The combination of a 5HT<sub>3</sub> receptor antagonist and dexamethasone when used for prophylaxis reaches an efficacy of 90% being PONV free.[23]

### Butyrophenones

Droperidol has until recently been the standard drug used for PONV. This changed dramatically when the American Food and Drug Administration added a black box warning to the package insert. The warning related to reports of prolonged QT interval syndrome associated with its administration and the potential for life threatening dysrhythmias. The warning also advised for prolonged EKG monitoring when droperidol was administered even at the low doses (0.625-1.25 mg) used for PONV. In several European countries droperidol was withdrawn. This action has led to a marked reduction in its use within the United States Its efficacy safety and cheap price remain and several articles and editorials have challenged the appropriateness of this warning. This will be discussed further in the section on controversies in PONV. As a prophylactic for PONV 0.625 mg appears to be the optimal dose (although 1.25 mg was slightly better for the

prevention of vomiting) and both doses had an efficacy similar to 4 mg ondansetron.[21]. The number needed to treat to prevent an episode of PONV compared to placebo is 5-7. Side effects are dose dependant. Below 2.5 mg both extra-pyramidal signs and sedation are extremely rare. Interestingly droperidol decreased the incidence of headache.[24].

### Benzamides

Metaclopramide although used for over 40 years is no longer a first line anti-emetic. In a meta-analysis of its use its efficacy was not much better than placebo. The number needed to treat to prevent an additional episode of PONV is 10.[25] Even when used in combination with another anti-emetic it does not tend to produce enhanced efficacy.

### Other

Anticholinergics (scopolamine), Antihistamines and Phenothiazines all have been used with varying enthusiasm for PONV. The scopolamine patch needs to be applied several hours prior to surgery for it to be effective in PONV. It does however provide a prolonged duration of action. The anti-histamines are rarely used as first line choices for prophylaxis of PONV largely because of their sedative effects. The phenothiazines however are the most commonly prescribed anti-emetics for post discharge PONV. Interestingly little data exists regarding both their efficacy and their optimal dose. When used in combined therapy they are generally administered with a 5 HT<sub>3</sub> receptor antagonist, dexamethasone or droperidol, however very little data is available on the use of such combinations.

Non-pharmacological means of treating PONV with acupuncture/acupressure or similar types of therapy have shown in the majority of studies to be more effective than placebo. The number needed to treat compared to placebo for the prevention of early PONV is 5.[26] A recent study has shown that when a relief band is combined with ondansetron it markedly improves both early and late PONV. [27].

An interesting new class of anti-emetics that may have the potential for use in PONV are the NK<sub>1</sub> receptor antagonists. Data thus far on their clinical utility is very limited but indicates that they may be extremely effective either alone or in combination especially for the prevention and treatment of vomiting.[28, 29]

### Present Controversies

Probably the most important controversy with respect to PONV is the role of prophylaxis. More recently the issue of QT prolongation has been the subject of several editorials and manuscripts. Lastly the question of repeat dosing with a 5 HT<sub>3</sub> receptor antagonist when the first dose fails is also uncertain.

### Prophylaxis

Probably the major driver in this controversy is the cost effectiveness of prophylaxis. Post-operative nausea and vomiting as stated above occurs in about 30% of patients. No single or combination treatment is 100% effective in treating PONV i.e. some patients receive prophylaxis without needing it whilst others need it and may still have PONV. The prevention of PONV however is very desirable amongst patients.. In

fact they are willing to pay \$100.[30] Scuderi however has demonstrate that treatment rather than prophylaxis is equally effective and produces similar patient satisfaction except in a sub-population of females with a previous history of PONV.[31] With these findings and a cost containment environment it behooves the clinician to make rational pharmaco-economic decisions. Based on a large multi-center study assessing the efficacy of ondansetron or droperidol compared to placebo, Hill et al calculated the incremental cost associated with achieving a PONV free patient. For the placebo group this cost was close to \$600 and was decreased to less than half of this for the active treatment arms. Most of the costs (70%–80%) were from nursing labor costs, from prolonged post-anesthesia care unit stay associated with persistent PONV or adverse effects of the anti-emetics.[32] Based on these data it would appear based on a cost benefit approach that prophylactic treatment of PONV is really only indicated in patients who are at increased risk. What constitutes risk? Apfel recently defined the major risk factors i.e. female gender, history of PONV or motion sickness, non-smoker, post-operative opiate administration.[7] More recently he has also added for early onset PONV the use of volatile anesthetics.[16] At least 1 of the factors noted above should be present. As 1 major risk factor only increases the risk of PONV by 10% probably a more rational approach is the presence of at least 2 risk factors where the risk of PONV increase from 10% to nearly 40%. As the increased cost of adding dexamethasone or droperidol to ondansetron (or other 5 HT blocker) is minimal whilst the reduction in PONV is markedly increased multi-modal therapy is probably preferable to mono drug therapy. This approach is largely in line with the recently published consensus guidelines discussed below.[33]

#### Prolonged QT Interval and Anti-emetics

This controversy was spurred by the Food and Drug Administration in the United States placing a black box warning on the package insert for droperidol. Droperidol at doses of 0.1 mg/kg is known to be associated with a prolonged QTc that may result in Torsades du Pointes. There have now been several editorials discussing the appropriateness of this Black Box warning and the true likelihood of arrhythmia's when administering low doses of droperidol as used for PONV.[34-37] All of these editorials have unanimously agreed that the safety and efficacy of droperidol has been well established and the warning is not truly warranted. Habib and Gan have presented the actual Medwatch reports that generated the warning. They state that the actual cause of the arrhythmia's that occurred in these cases is confounding and conclude that in none of the cases in which arrhythmias occurred after small doses of droperidol (1.25 mg or less) was there evidence of a cause-and-effect relationship.[38]

Interestingly in one of the patients included in the Habib report dolasetron was also given. The 5 HT<sub>3</sub> receptor antagonists also produce prolongation of the QT interval through the blockade of Na channels. The 5 HT<sub>3</sub> receptor antagonists are metabolized by CYP2D6 and CYP3A subfamily.[39] Dolasetron is metabolized to an active metabolite, hydrodolasetron. There is significant variation in the metabolic activity of these enzymes leading to either increased accumulation of the drug where the enzymes are decreased or decreased activity or increased metabolites. The effect of this class of drugs on the Na channel is dose dependant. Ondansetron is the least potent followed by hydrodolasetron

and then granisetron. However based on dosing Dolasetron (through its metabolite) produces the greatest inhibition followed by ondansetron and then granisetron.

### Repeat Dosing of 5 HT<sub>3</sub> Antagonists

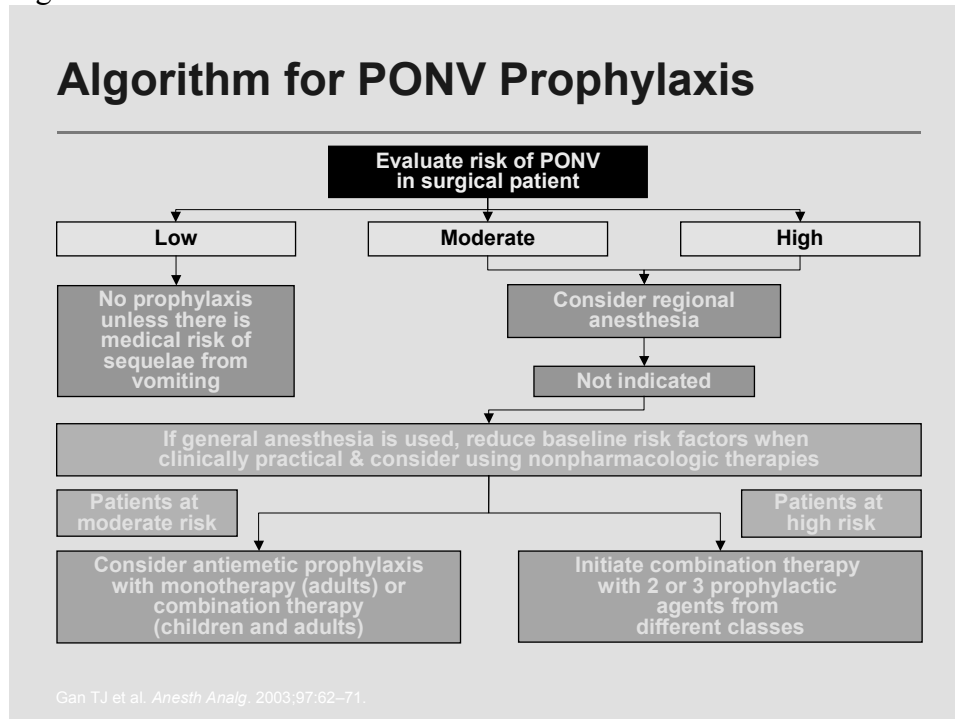
In virtually all studies of the 5 HT<sub>3</sub> receptor antagonists for PONV they all seem to reach a ceiling effect and this generally is the dose recommended for prophylaxis of PONV. For example little advantage has been seen when administering greater than 4 mg of Ondansetron or 12.5 of Dolasetron for PONV. It has also been shown that 4mg of Ondansetron given for failure of an initial dose of 4 mg Ondansetron has no greater efficacy than placebo.[40] In 2 interesting studies in patients treated for chemotherapy granisetron was effective in over 50% of patient who failed to respond to ondansetron.[41, 42] Thus there may be some value to follow ondansetron failure with granisetron.

### Therapeutic Guidelines

PONV is an undesirable outcome of anesthesia and surgery that creates considerable patient distress even though it is rarely associated with significant morbidity. Its cause are multi-factorial. The financial impact of PONV and its treatment on health care dollars is significant. The literature is replete with articles assessing interventional therapies for the prevention of PONV but investigation of overall strategies to rationalize therapeutic approaches for each individual patient is limited. Recently a number of authors (who have published extensively in the area of PONV) have written a consensus document outlining practice guidelines for PONV.[33] The first therapeutic goal is to reduce baseline risk for PONV. These measures include insuring adequate hydration, minimizing anxiety, avoiding nitrous oxide, avoiding or minimizing opioid use, avoiding high dose reversal of a neuromuscular antagonist, using high concentrations of oxygen and the use propofol as the preferred anesthetic. Therapeutic interventions have been divided into first and second line treatments. (Table 1) First line therapy includes the 5 HT<sub>3</sub> receptor antagonists, dexamethasone and droperidol.

The authors of the consensus document have also developed an algorithm for PONV prophylaxis. (Figure 2) Essentially there are no recommendations for patients at low risk. For patients at moderate risk the recommendation is to reduce the baseline risk and consider prophylactic mono or multi-modal therapy with a first-line drug. For patients at high risk; decrease baseline risk and provide prophylaxis using multi-modal therapy

Figure 2.



For patients who subsequently develop PONV despite following the algorithm they have also provided therapeutic guidelines (Table 2). Where prophylaxis has not been given it is recommended to administer a first line drug, where prophylaxis has been given within the first 6 hours following surgery an alternative first line drug or second line therapy should be given. Where PONV occurs after 6 hours the initial therapy can be repeated. At present for out patients, as first line therapies are largely given intravenously (with the exception of oral disintegrating ondansetron), second line therapies are used. Interestingly the dose and efficacy of these second line therapies are far less established. The most commonly used second line therapies are prochlorperazine and promethazine. The scopolamine patch is also increasing in popularity.

Post-operative nausea and vomiting is distressing for patients. As its etiology is multi-factorial it is incumbent on the anesthesia provider to have a sound knowledge of its patho-physiology and the available therapeutic modalities to both minimize its incidence and to provide effective prophylaxis and treatment. Following recommended guidelines it is likely that PONV can be reduced in all patients from a present incidence of approximately 30% to less than 10%.

Table 1

## Antiemetic Therapy for PONV Prophylaxis in Adults

### FIRST LINE

- 5-HT<sub>3</sub> antagonists
  - Ondansetron
  - Dolasetron
  - Granisetron
  - Tropisetron\*
- Dexamethasone
- Droperidol

### SECOND LINE

- Dimenhydrinate
- Ephedrine
- Prochlorperazine
- Promethazine
- Scopolamine
- Nonpharmacologic techniques
  - Acupuncture
  - Hypnosis

\*Currently not FDA-approved for PONV in the US

Adapted from Gan TJ et al. *Anesth Analg*. 2003;97:62–71.

Table 2

## PONV Treatment in Patients Who Did Not Receive Prophylaxis or in Whom Prophylaxis Failed

None or dexamethasone	Administer low-dose 5-HT <sub>3</sub> RA*	IIA
5-HT <sub>3</sub> RA	Use agent from different class	V
Combination therapy with 5-HT <sub>3</sub> RA* (when PONV occurs <6 hrs postop)	Do not repeat initial therapy	IIIA
	Use agent from a different class	V
	Use propofol, 20 mg PRN	IIIB
Combination therapy with 5-HT <sub>3</sub> RA* (when PONV occurs >6 hrs postop)	Repeat 5-HT <sub>3</sub> RA* (not dexamethasone and scopolamine)	V
	Use agent from different class	V

\*Low-dose 5-HT<sub>3</sub> RA dosing (dolasetron 12.5 mg; granisetron 0.1 mg; ondansetron 1 mg; tropisetron 5 mg)

Adapted from Gan TJ et al. *Anesth Analg*. 2003;97:62–71.

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