Postoperative Nausea and Vomiting (PONV)

Perioperative Management of PONV

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PONV

- During the "ether era" of anesthesia & then cycloproprane anesthesia
  - PONV was expected to occur – it was the norm
  - PONV rates of 60 to 80% were very common
- We now have anesthetic agents that reduce the risk of PONV
  - TIVA anesthesia – especially Propofol (at least in PACU)
- We also have antiemetic agents that prevent and provide rescue from PONV
  - Short acting, established agents – effective for 0 to 24 hrs.
  - Newer, longer acting agents – effective for 24 to 72 hrs.
  - Agents that act on newly discovered receptor sites
  - Mutimodal therapy for high risk patients

Categories of PONV

- PONV can be categorized into several distinct periods of time
  - 0 to (2 – 6) hours: early PONV
  - 6 to 24 hours: late PONV
  - 24 to 48 hours: delayed PONV
  - Highest likelihood of PONV is in 1st 24 hrs.
    - 0 to 2 hours is prime time for PONV
      - inhalation agents are usually responsible
      - TIVA (propofol): less likely to cause PONV in PACU
    - significant decrease in PONV after 24 hrs.
    - possible to persist for up to 5 days

Am J Health-Syst Pharm. 2009; 66: S3

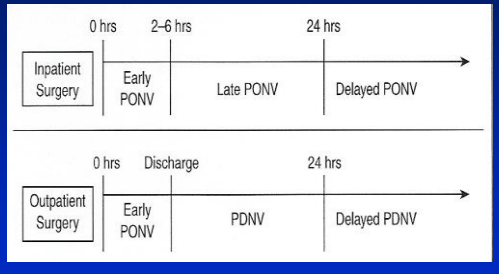
Anesth Analg. 2007; 105: 1615

Categories of PONV

- PDNV (post discharge nausea & vomiting)
  - discharge from ambulatory center
  - discharge from oral surgery office
  - 2 components to PDNV
    - N/V in PACU – office recovery area
    - N/V after arrive home
    - ***if have N/V in recovery, 3 times as likely to have PDNV at home***

Anesthesiology. 2012; 117: 475

PONV vs PDNV



Am J Health-Syst Pharm. 2009; 66(1): S3

Opioid Induced Nausea & Vomiting (OINV)

- Opioids
  - directly stimulate CTZ
  - decrease gastric motility
    - prolongs emptying time
    - fluids remain in stomach for vomiting
- Opioids also sensitize otic & vestibular areas
  - leads to motion sickness, nausea, & vomiting
  - *immobile patients less likely to have OINV*
- OINV typically lasts for ~ 2 days & stops

Andersen & Krohg. Can Anaesth Soc J. 1976; 223: 366

Clinical Consequences of PONV

- PONV has been called the " big little problem"
  - mortality would be highly unlikely
  - morbidity may be transient with little significance, or it can pose significant problems for the patient
    - may compromise the healing & results of the surgery
    - may regret having the procedure done, especially if it was elective surgery
    - may not consent to future procedures that would be necessary to complete the treatment plan
    - could lose other potential patients because of their dissatisfaction

Clinical Consequences of PONV

- Metabolic Complications
  - electrolyte imbalances & dehydration
- Physiologic Complication
  - esophageal tears, fractures, wound dehiscence, and malnutrition
- Psychological Complications
  - anxiety, depression, and noncompliance of therapy
- Financial & Social Complications
  - delay in return to normal, daily functions
  - delay in return to work

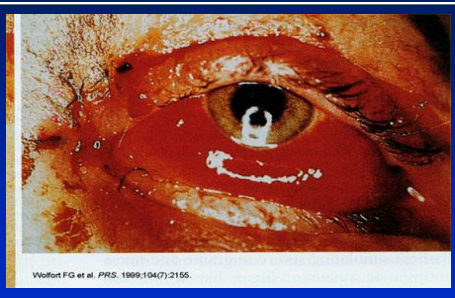
Am J Health-Syst Pharm. 2009; 66: S11

Clinical Consequences of PONV

- Pulmonary aspiration of gastric contents
- Intraocular hemorrhage & vision loss
- Subcutaneous emphysema & airway compromise
- Patient and family dissatisfaction not only with the surgery but with the surgeon as well
  - complaints to referring doctor
  - explain problem to the patient, the family, & the referring doctor
- May need to return to office or emergency room for fluids & rescue medications

Kovac. Drugs. 2000; 59: 213 Anesth Analg. 2007; 105: 1615

Retrobulbar Hematoma



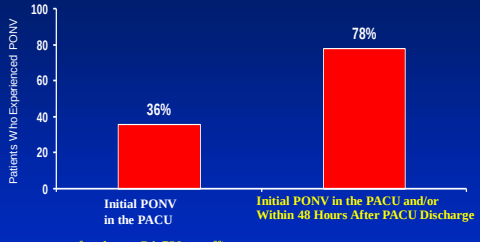
Medscape Today 2007

Incidence of PONV

- In general, surgery without PONV prophylaxis
  - incidence has decreased to **20 to 30%**
- Patients with a high risk (3 or more)
  - incidence range is still **70 to 80%**
- Each episode of PONV delays discharge from PACU by about 20 min
- PONV may last for up to 5 days
  - may be PONV, PDNV, or OINV or combinations of all three

Anest Analg. 1995: 80; 903 Anest Analg. 2003: 97; 62 Anest Analg. 2002: 94; 1199

PONV Occurring in the PACU* and/or Within 48 Hours After PACU Discharge



- Most cases occur after leave PACU or office
- ***78% of PONV cases occur in first 48 hours***
- Antiemetics that are effective for **0 to 48 hrs.** would benefit our patients

* PACU=postanesthesia care unit.
Carroll NV et al. *Anesth Analg*. 1995;80:903–909. Source: Medscape Today 2007

PDNV versus PONV

- Is PDNV different from PONV?
- Are the risk factors the same?
- Are patients concerned about PDNV?
- Should the surgeons & anesthetists be concerned about PDNV?
- Are prophylactic and rescue therapies the same for both?

Outpatient PDNV

- ≥ 60% of all surgery is done in the ambulatory setting
  - ~ 34 million cases of outpatient surgery
  - expect those numbers to increase
- Outpatient surgery risk of PDNV ~ 30 to 50%
  - reports of nausea 56.9%
  - reports of vomiting 19.4%

Location	Nausea	Vomiting
PACU	22.6%	19.4%
Ride Home	34.7%	8.1%
Day of Surgery: at home	44.8%	13.3%
Post op: Day 1	25%	5.2%

Anesth Analg. 2007; 105: 1615 ASA Refresher Courses. 2009; 37(1): 69-80
J Clin Anesth. 2013; 25: 551 J. Clin Anesth. 2013;25:551

PDNV (Post Discharge Nausea & Vomiting)

- Ambulatory anesthesia
  - surgical procedures are often shorter duration than inpatient surgery
    - less exposure and lower doses of emetogenic agents
      — typically: inhalation agents & perioperative opioids
    - incidence of N/V: inhalation > balanced > TIVA
  - forced, early ambulation
    - "office oral surgery fast tracking"
    - "dragging" the patient from the chair to recovery
    - too much, too soon = nausea & vomiting
  - pain
    - risk factor for PDNV for 0 to 7 days
      — may be from ↑ use of opioids

J. Clin Anesth. 2013;25:551
Anesth Clinics. 2014;32:505

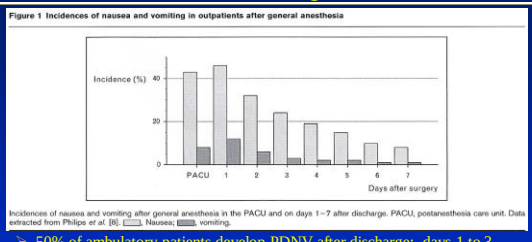
PDNV (Post Discharge Nausea & Vomiting)

- Ambulatory Anesthesia Risk Factors
  - forced, early PO intake in PACU prior to discharge
    - limiting PO fluids ineffective in reducing emesis in children
    - may be a factor in adolescents & adults
  - holding IV fluids perioperatively: (hep lock or kvo)
    - fluids make a patient feel better & less N/V
  - car motion sickness
    - rough ride home; vestibular activation = N/V
    - increased risk if also have PO fluids on board
  - no antiemetics perioperatively
    - TIVA is your only antiemetic

PDNV (Post Discharge Nausea & Vomiting)

- Ambulatory Anesthesia
  - Short acting antiemetics
    - may not have N/V in PACU
    - experience N/V at home due to short half life drug
  - Patients at home have no access to fast acting IV antiemetic rescue
  - Patients may not tolerate PO antiemetics
    - vomit them up before they can be absorbed
    - rectal administration = poor acceptance
    - options are limited once patient is at home

Ambulatory Surgery Nausea & Vomiting



- 50% of ambulatory patients develop PDNV after discharge: days 1 to 3
- Nausea on day #1 was 46%
- Nausea on day #7 was 8%
- Vomiting on day #1 was 12%
- Vomiting on day #7 was 1%
- Longer acting agents would be useful

Curr Opin Anaesthesiol. 2009; 22: 532-538

PDNV

- Apfel et al: 2170 outpatient general anesthesia cases
  - Inhalation only or balanced anesthesia
    - propofol + sevoflurane (66.4% cases) maintenance
    - no TIVA cases
  - 77.4% patients received prophylactic 5-HT3 agents
    - ondansetron in all but 2 cases
    - 34.5% cases: 2 antiemetics used
    - 12.1% cases: 3 antiemetics used

Anesthesiology. 2012; 117: 475 (Multi center study)

PDNV in Apfel Study 2007-2008

- Incidence of Nausea & Vomiting in PACU
  - 19.9% Nausea only
  - 3.9% Vomiting only
  - ***20.7%*** ***Nausea & Vomiting***
  - 3.6% Severe nausea
  - 0.2% Severe vomiting
- Incidence of PDNV from discharge to 48 hrs.
  - ***37.1%*** ***Nausea & Vomiting***
  - 36.6% Nausea only
  - 11.9% Vomiting only
  - 13.3% Severe nausea
  - 5.0% Severe vomiting

Risks of PDNV for 0 to 48 hours

PDNV in Apfel Study 2007-2008

- Apfel results
  - 37.1% incidence correlates to the 35% incidence reported by Carroll et al in 1995
- Only 4.4% of patients had antiemetic prophylaxis acting long enough to prevent PDNV after discharge
  - need to rethink agents we use
  - consider longer acting agents

Anesthesiology. 2012; 117: 475
Anesth Analg. 1995; 80: 903

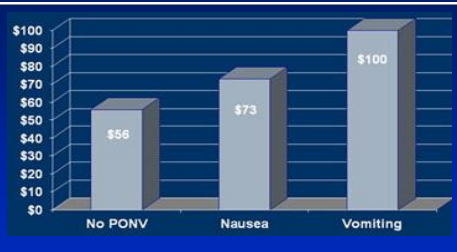
PONV: An Undesirable Consequence of Surgery

- Patients rank vomiting as the most undesirable outcome, even more undesirable than pain.

Patient Ranking	
Rank	**Postoperative Anesthesia Outcomes**
1	***Vomiting***
2	Gagging on endotracheal tube
3	Incisional pain
4	***Nausea***
5	Recall without pain
6	Residual weakness
7	Shivering
8	Sore throat
9	Somnolence

Macario. *Anesth Analg.* 1999;89:652–658. Source: Merck Medical Forums 2007. Emend presentation

Patients are " willing to pay "



- Patient survey about how much they would pay out of pocket to avoid PONV
- There is no way this study was done in Pittsburgh: " will my insurance cover this?"

Gan. Anesth Analg. 2001: 92; 393 Medscape Today 2007

Nausea

- Subjective sensation of an urge to vomit
- Associated with increased salivation
- Patients may have pallor, sweating, & bloating
- See an increase in swallowing
- Decrease in gastric motility

Retching

- Unproductive effort to vomit
- Rhythmic contraction of diaphragmatic, abdominal, and intercostal muscles
- Stirs the gastric contents in the stomach
- Small intestines contract to prevent gastric emptying
- "Dry heaves"

Vomiting

- Coordinated contraction of abdominal, intercostal, and diaphragmatic muscles
- Relaxation of the esophageal sphincter
- Closure of the glottis
- Elevation of the soft palate
- Forceful expulsion of gastric contents into the oropharynx and/or nasopharynx

Regulation of Vomiting

- Vomiting Center (VC) is in the lateral reticular formation of the medulla adjacent to following areas
  - 4^{th} ventricle of the brain
  - the nucleus tractus solitarius
  - the area postrema at the level of the motor nucleus of the vagus
- VC receives afferent inputs
  - peripheral and central
- VC controls the efferent response of vomiting

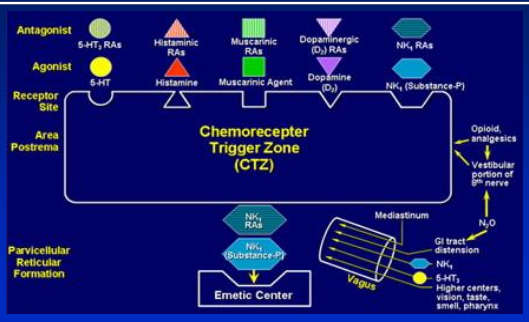
Afferent Inputs for Vomiting

- Higher cortical centers
  - triggered by sight, smell, stress, and anxiety
  - memory of previous episodes of nausea & vomiting
- Vestibular apparatus pathway to the cerebellum
- Vagal & glossopharyngeal nerve afferents
- CTZ afferents
- Peripheral afferents especially in the GI tract
  - high concentration of serotonin
  - serotonin can be blocked by the 5-HT_3 agents both centrally and peripherally
    - 1^{st} generation 5-HT_3 antagonists work better at peripheral sites

Chemoreceptor Trigger Zone (CTZ)

- CTZ is in the area postrema in the floor of the 4^{th} ventricle at the base of the medulla
- Multiple receptors sites for nausea and vomiting in the CTZ
  - histamine, serotonin, cholinergic-muscarinic, and dopamine D_2 receptors
  - new site: neurokinin-1 sites
- CTZ stimulates the Vomiting Center

CNS Receptors for Nausea and Vomiting



Medscape Today 2007

Apfel Risk Factors for PONV

Apfel Risk Factors	Points
Female Gender	1
Non Smoker	1
History of PONV	1
Post operative Opioids	1
Total Points	0 to 4

- Low risk of PONV 0 to 1
- Moderate risk PONV 2
- High risk PONV ≥ 3

PONV Risk Factor Significance

Order of Risk: Highest to Lowest	Risk Factor
#1	Female Gender
#2	History of PONV
#3	Non Smoker
#4	History of Motion Sickness
#5	Age of Patient

Anesth Analg. 2014; 118: 85-113

Risk Factors for PONV

- Female
  - primary risk factor for PONV
- History of PONV or motion sickness
- Non smoker
- Postoperative opioids
- Younger age
- General vs regional anesthesia
- Volatile anesthetics and nitrous oxide
- Duration of anesthetic

Apfel. Anesthesiology. 1999: 91; 693 Anesth Analg 2007; 105: 1615
Anesth Analg. 2014; 118: 58-113 Anesth Analg. 2014: 118

PONV Risk Factor: Female

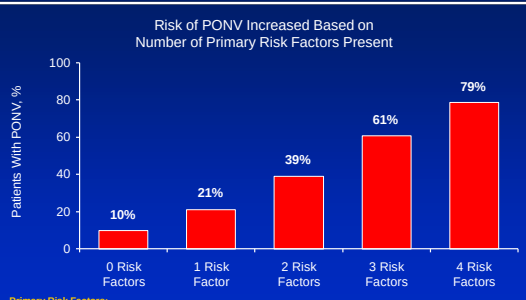
- Post puberty females have 2 to 3 times the risk as a male
- Phase of menstrual cycle has no effect on PONV
- Risk decreases after age 70
- Vomiting is more severe than in males
- Concern is that females are majority of "cosmetic surgery population"

ASA Refresher Course. 2009; 37(1)

Smoking and PONV

- Smokers are a lower risk for PONV
- Smoking induces cytochrome P450 enzymes
  - increase metabolism of volatile anesthetics and other agents used during the anesthetic
- No antiemetic substance contained in tobacco
  - patient may smoke something else before surgery that can prevent PONV, but we can not recommend it.
    - AT LEAST AT PRESENT

Impact of Multiple Patient-Related Risk Factors*



Primary Risk Factors:
Female sex • History of PONV or motion sickness • Nonsmoking • Use of postoperative opioids
Patients with 2 or more risk factors should receive prophylactic antiemetics

* Validated in 2,722 adult patients receiving inhalational anesthesia.
Apfel CC et al. *Anesthesiology*. 1999;91:693–700. Source: Merck Medical Forums 2007

Anesthetic Risk Factors for PONV

- Compared to local anesthesia, general anesthesia is ***9X more likely*** to cause PONV
- Anesthetic volatile gases as sole agent
  - primary cause of early PONV 0 to 6 hours
  - minor impact on PONV over next 7 to 24 hours
  - longer the exposure to gas
    - greater the risk due to increased dose
  - no difference in which gas is used
- Less of risk if use balanced anesthesia
  - IV agent induction & volatile agent maintenance
- Lowest risk if use TIVA

Anesthesiology. 1999: 91; 109 Anest Clinic N. Am. 2003: 21; 347 Anesth Analg 2007: 105

Anesthetic Risk Factors for PONV

- Intra operative opioid use
  - low dose opioids
    - do not increase the incidence of nausea & vomiting
    - low dose fentanyl = 0 to 2 mcg per kg
    - 100 mcg of fentanyl is equivalent to 10 mg morphine
    - 100 mcg fentanyl is equivalent to 75 mg meperidine
    - no significant histamine release at 50 mcg/kg fentanyl

Type of Opioid Used

- Flacke et al. Anesth Analg. 1985
  - No difference between morphine, demerol, sufentanil, or fentanyl during balanced anesthesia
- Jellish et al. Otolaryngol Head & Neck 2000
  - ear surgery: fentanyl bolus vs remifentanil infusion PONV rates were similar
- Davis et al. Anesth Analg. 2000. T&A surgery
  - no difference in PONV between remifentanil & fentanyl
  - did use ondansetron and decadron intraoperatively

Type of Opioid Used

- Eltzschig et al. Anesth Analg. 2002
  - strabismus surgery: incidence of PONV with remifentanil & fentanyl ~ 50% (is it the opioid or the surgery?)
    - remifentanil had less episodes per patient
- Acta Anaesthesiol Scand. 2005.
  - TIVA anesthesia with remifentanil or fentanyl
  - No differences in PONV
    - 0 to 2 hrs and 12 to 24 hrs
  - Differences in PONV during hours 2 to 12 postop
    - Higher PONV in fentanyl group
- N Eng J Med. 2004: 5199 pts no difference in PONV
- Conclusion: type of narcotic does not make a difference

Anesthetic Risk Factors for PONV

- Etomidate and ketamine
  - do increase the risk of PONV
- Pentothal and Brevital
  - have less emetogenic potential than above
  - if you add ketamine to the anesthetic, get an additive risk of nausea and vomiting

Anesthetic Risk Factors for PONV

- Nitrous oxide at levels > 40%
  - PONV risk is ~ 10 to 15%
  - nitrous oxide risk is independent from the risk of volatile agents
    - they are not additive or overlapping
  - low risk patients, nitrous is not a factor
  - recent OR trends, see less use of nitrous anyway
  - Is nitrous still an effective agent in 2015?

Surgical Risks for PONV

- Duration of surgery > 30 mins
  - see 59% increase for each additional 30 mins of surgery time
  - if you felt the patient had a 20% risk of PONV, now add 20 + (20 X .59) for each additional 30 mins.
- Throat packs with light anesthesia
  - stimulate gag reflex
- Swallowing blood & irrigation during the surgery
  - < 1 oz of blood can increase risk of N/V
  - routine use of NG tubes for non head & neck surgery does not decrease the risk of PONV

Type of Surgery

- Conflicting reports in literature
- Some feel the type of surgery does affect the incidence of PONV
- Others believe PONV only depends upon specific patient and anesthesia factors
- Ruiz et al.
  - reported that neurosurgery, head & neck including intraoral surgery, and abdominal surgery had the highest risk of PONV
  - greater incidence of antiemetic rescue in 1st 0 to 2 hours postoperatively

Anesth Analg. 2010; 110; 403-409

Third Molar Surgery

- Third molar surgery with no antiemetic prophylaxis under GA: 20 to 40% risk of PONV
  - nausea 15 to 20%
  - vomiting 5 to 8%
- Incidence of PONV justifies the use of prophylactic antiemetics
  - number of agents depends upon patient's risk & type of anesthesia you use in the office
  - your office incidence and your PDNV incidence also play a role in number & type of agents used

JOMS. 2002; 60(11): 1246 Br J OMFS. 2008; 46: 207

Orthognathic Surgery

- Silva et al. 514 patients treated by maxillary and/or mandibular osteotomies
- 40.08% incidence of PONV (206 / 514)
  - 25.29% PONV in PACU (130 / 514)
  - 9.53% PONV in SSU (49 / 514)
  - 5.25% PONV in PACU + SSU (27 / 514)
- Mandibular osteotomies
  - Went to PACU for 2 hrs, the SSU or discharge
- Maxillary & double jaw cases
  - Went to PAC for 2 hrs, then SSU for overnight

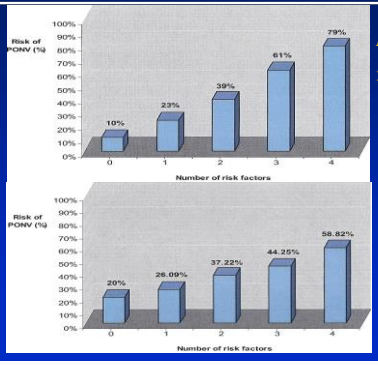
Orthognathic Surgery

- Risk factors from their study
  - Ages 15 to 25 yrs old greater incidence of PONV
  - Surgical procedures ***> 1 hour***
    - Bimaxillary surgery > maxillary > mandibular rates of PONV
  - Use of any inhalation agents for anesthesia

Orthognathic Surgery

- Risk factors from their study
  - Postoperative opioids
    - 2.7 X more likely to cause PONV than non- opioids
    - intraoperative opioids
      - not statistically related to PONV
  - Postoperative pain levels correlated with PONV rates
    - only studied in PACU
  - Predisposing factors as reported elsewhere in literature
    - Females, nonsmokers, prior history of PONV or motion sickness, & migraines
    - Correlates with Apfel risk factors

Orthognathic Surgery



Apfel Risk Factors for PONV

- multiple references cited in literature

Silva et al. JOMS. 2006

- ***mutiple risk factors in any patient will increase the risk of PONV***
- PDNV rates were not studied in this report
- PONV rates for 0 to 24 hrs reported in study

Cosmetic Surgery: High Risk PONV

- Breast augmentation surgery: 37 to 59% risk
  - 42% in recovery 43% 24 hours later as PDNV
  - see more surgeons using either TDS patches or ondansetron ODT postoperatively especially for ambulatory surgery
- Facial rejuvenation surgery
  - rhytidectomy, endoscopic brow lifts, & platysmaplasty
  - OMFS office cosmetics are candidates for TDS or ODT postoperatively

Marcus. Plast Reconst Surg. 2002: 109; 2487

Disproven Risk Factors or Techniques to Reduce Risk

- BMI
- Anxiety
- Migraine headaches
  - increased incidence of nausea but not vomiting
- Perioperative Fasting Time
- NG tube decompression of gastric contents
- Use of supplemental oxygen to reduce PONV

ASA Refresher Course in Anesthesiology. 2009; 37(1) 69-80
Anesth Analg. 2014; 118

Possible Risks but Conflicting Data

- Menstrual Cycle
  - 1st week felt to be risk factor, but other data no effect
- ASA status of patient
- Level of anesthetist's experience

PONV IN CHILDREN

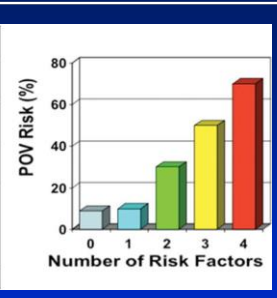
PONV Risk for Children

Risk	Points	Vomit
No risk	0	9%
Sx > 30 mins	1	10%
Age ≥ 3 yrs old	2	30%
Strabismus sx	3	55%
History of PONV or history of PONV in parent or sibling	4	70%

- Remember, hard to assess nausea in a child, you only estimate vomiting risk
- Eberhart Risk Scale for children

Eberhart Risk Score Children

Risk Factors	Points
Surgery ≥ 30 min.	1
Age ≥ 3 years	1
Strabismus surgery	1
History of POV or PONV in relatives	1
Sum =	0 . . . 4



Anesth Analg. 2014; 118

PONV in Children

- PONV in children twice as common as in adults
- High risk patients: use 2 to 3 agents to reduce risk of PONV
- Ondansetron is the 1st line drug of choice
  - dexamethasone is equally effective as a prophylactic agent
- Age < 3 y.o. low risk PONV ~ 5 to 20%
- Age 3 – 14 y.o. incidence of PONV increases
  - 42 to 51% incidence
  - 0.2 to 0.8% increase per year until puberty
  - peaks at about age 14

Anesth Analg. 2014; 118

Pediatric PONV

After age 3, see a range of 42 to 51% Peaks at age 14

Rowley. Anesth Intensive Care. 1992: 10; 309 Medscape Today 2007

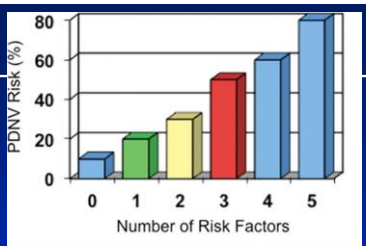
PDNV

PDNV Risk Factors

- Female
- Age < 50 years old
- History of PONV with previous surgery
- Opioids in PACU
- Nausea in PACU

Apfel study 2007-2008

PDNV



Risk Factors	Points
Female sex	1
History of PONV	1
Age <50 years	1
Use of opioids in the PACU	1
Nausea in the PACU	1
Sum	**0…5**

Anesth Analg. 2014;118

Incidence of PDNV

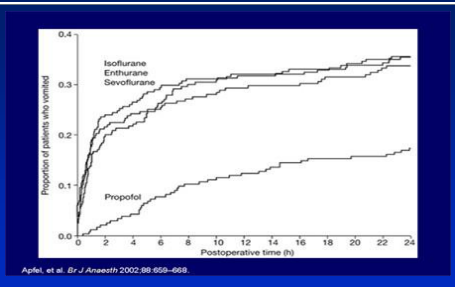
Number of Risk Factors	% Incidence
0	10%
1	20%
2	30%
3	50%
4	60%
5	80%

Apfel et al. Anesthesiology. 2012; 117: 475

Modify Anesthetic Risks

- TIVA with propofol
  - Propofol has antiemtic properties
    - reduces risk of PONV by ~ 19%
  - If you use Propofol and oxygen / air instead of nitrous oxide, see a reduction of ~ 25%
  - Use of propofol for maintenance has the greatest impact of all the drug strategies in reducing early PONV
    - effective for few hours usually not effective post discharge

Volatile Agents versus Propofol



- Propofol has lower risk of PONV especially in 1st few hours

Medscape Today 2007

Modify Anesthetic Risks

- Midazolam
  - decreases anxiety
    - anxiety was thought to be a risk for PONV
      - — not uncommon to see CINV when patients just see the office where they will receive the chemotherapy
  - antiemetic effect on cortex
  - 2 mg IV at end of surgery can reduce risk of PONV
- Profound local anesthesia
  - Pain can cause nausea & vomiting

IV Fluid Maintenance 4 – 2 – 1 Rule

Body weight (kg)	Fluid rate (mL/kg)	Weight category (kg)	Fluid maintenance rate (mL/h)
0-10	4	10	40
11-20	2	10	20
21+	1	50	50
Total		70	110

- Calculation for a 70 kg patient: requires 110 mls per hour NPO
- Dehydration & hypovolemia may be factors for PONV
- Most clinicians believe that fasting patients are hypovolemic preoperatively
- Recent research has shown that healthy patients are usually normovolemic even after prolonged NPO periods

Acta Anaesthesiol Scand. 2008; 52: 522-529

IV Hydration & PONV

- Multiple recommendations for preoperative rehydration
  - 2 mls/kg/hr is widely accepted
    - 70 kg NPO for 6 hrs. = 70 X 2 X 6 = 840 mls fluid
  - Bennett et al. 1-2 mls/kg vs 16-17 mls/kg
    - ASA 1 & 2 patients for third molar surgery
    - decreased adverse outcomes: less fatigued, less drowsy, & improved sense of well being for 16-17 mls/kg group
    - no difference in PONV reported between groups

Lambert. AANA J. 2009; 77: 110 Bennett. OOO. 1999; 88: 279

IV Hydration & PONV

- Maharaj et al. large volume vs small volume
  - 2 mls/kg/hr fasting vs 3 mls/kg infused 20 mins before induction on ambulatory surgery patients
  - incidence of PONV reduced over 72 hrs
  - frequency of moderate to severe nausea reduced
  - saw decreased postoperative pain & opioid requirements
  - result: they recommend the use of 2 mls/kg/hr fasting as fluid replacement preoperatively

2 mls/kg/hr fasting for fluid replacement in ambulatory surgery

Maharaj. Anesth Analg. 2005; 100: 675-82

IV Hydration & PONV

- Holte et al. Elective fast track surgery
  - minor to moderate non cardiac surgery
    - perioperative fluids > 1 liter improved recovery
    - no data to support any one type of fluid
  - minor non cardiac surgery
    - optimal amount of fluid to enhance recovery is yet to be determined reasonable ~ 1 liter

J Am Coll Surg. 2006; 202: 971

IV Hydration & Office Surgery

- Healthy patients for third molar surgery
  - minimum of 500 ml of NSS or LR
  - general surgery data
    - 1 liter fluid = less PONV
  - if use 1 liter fluid
    - infuse no more than 500 ml under general
    - infuse remainder when ambulatory
      - patient may need to void
    - less need for rescue agents if use D5NS or D5LR
      - 50 grams dextrose in 1000 ml fluid given in PACU

Dabu-Bondoc. Anest Analg. 2012: Dextrose reduces antiemetic rescue in PACU.

Modify Anesthetic Risks

- Neostigmine for reversal of NMB agents
  - dose > 2.5 mg has been shown to increase risk of PONV
  - reducing the dose to < 2.5 mg did reduce risk of PONV
  - recent data: questions if neostigmine is a risk at all
    - minimizing the dose is no longer a strategy to reduce PONV
- Oxygen ≥ 80% during surgery or in PACU will not reduce the incidence of PONV
  - No difference as compared to 30 or 40% oxygen
  - No effect on nausea, but may decrease early vomiting
  - Not used to prevent PONV

Anesth Analg. 2014;118

Modify Anesthetic Risks Summary

- Avoid inhalation anesthetics
- Avoid nitrous oxide
- Use Propofol for induction and maintenance
- Adequate hydration
- Intraoperative low dose opioids
- Minimal postoperative opioids
- Assess the patient's risk factors, intraoperative opioid and ketamine use, hydrate, and minimize postoperative opioids.

Post Operative Risks for PONV

- Pain & dizziness
- Moving the patient quickly or sharp bends on transporting the patient
- Opioids & hypovolemia
- Forced early ambulation
  - "dragging the patient from the dental chair" to recovery – "oral surgery fast tracking"
- Forced early PO intake liquids
  - tell patient they can drink when they get home
- Oral solid foods too early
  - tell patient liquids for ~ 2 hours
  - slow intake of solids for 1st 8 hours

Postoperative Opioid Use & PONV

- Pain by itself is a risk for PONV
  - most cases will require opioid use
- Use of opioids **doubles the risk** of PONV
- *Lower the dose…… lower the risk of PONV*
- Risk of postoperative opioid use on PONV over 0 to 24 hours
  - Nausea 51.3%
  - Vomiting 23.8%
- If a patient does not develop OINV in first 24 hours
  - risk of OINV > 24 hours is unlikely

Postoperative Narcotic Use & PONV

Drug	Oral dose	Parenteral dose
Alfentanil		10 μg
Codeine	20 mg	13 mg
Fentanyl		10 μg (=10 μg epidural)
Morphine		1 mg (= 10 μg spinal)
Oxycodone	2 mg	
Pethidine		7.5 mg
Tramadol	20 mg	10 mg

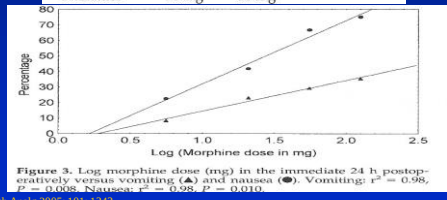
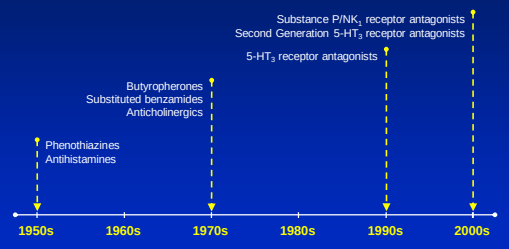


Figure 3. Log morphine dose (mg) in the immediate 24 h postoperatively versus vomiting (▲) and nausea (●). Vomiting: $r^2 = 0.98$, $P = 0.098$. Nausea: $r^2 = 0.98$, $P = 0.010$.

Anesth Analg 2005; 101: 1343

Antiemetic Medications

Antiemetic Evolution Timeline



Source: Merck Medical Forums 2007

Classification of Antiemetic Agents

5-HT-3 Receptor Antagonists	**Ondansetron (IV and ODT)** **Palonosetron (Aloxi)** **Ramosetron (Nasea)**
NK-1 Receptor Antagonists	**Aprepitant (Emend)**
Phenothiazines	**Prochlorperazine (Compazine)** **Promethazine (Phenergan)**
Corticosteroids	**Dexamethasone (Decadron)** **Methylprednisolone**
Anticholinergics	**Scopolamine TDS patches**
Antihistamines	**Diphenhydramine (Benadryl)** **Dimenhydrinate (Dramamine)**
Butyrophenones	**Droperidol**
Benzamides	**Metoclopramide**

CTZ Receptor Site Affinity

Drugs	Dopaminergic D2	Muscarinic Cholinergic	Histamine H1	Serotonin 5-HT-3	NK-1
Phenothiazines	++++	+/++	++/++++	+/-	--
Butyrophenones	++++	--	+	+/-	--
Antihistamines	+/++	++	++++	--	--
Anticholinergics	+	++++	+	--	--
Benzamides	+++	--	+	++	--
5-HT-3	--	--	--	++++	--
NK-1	--	--	--	--	++++

White. Anesthesiology. 1992; 77: 162 (not for NK-1 data)

Common Side Effects of Antiemetics

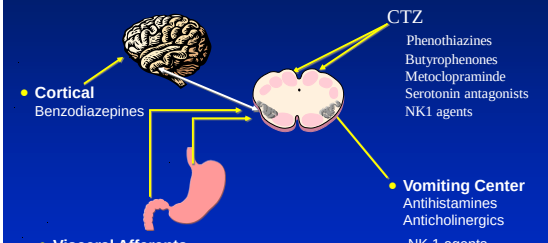
NK-1 Antagonists	Diarrhea, dizziness, fatigue, headache, & hiccups
5-HT-3 Antagonist	Headache, dizziness, constipation, & diarrhea
Dexamethasone	GI irritation, anxiety, insomnia, hyperglycemia, & perineal itch (rapid injection)
Phenothiazines	Restlessness, diarrhea, agitation, dysphorias, sedation, hypotension, extrapyramidal reactions, SVT, & NMS (rare)
Phenergan	In addition to typical phenothiazine side effects; tissue necrosis & nerve injury in extravasation sites

Common Side Effects of Antiemetics

Anticholinergics	Dry mouth, blurred vision, dizziness, & urinary retention
Butyrophenones	Sedation, confusion, dysphoria, extrapyramidal reactions, & possible torsade de pointes
Antihistamines	Sedation, prolonged recovery, dry mouth, blurred vision, confusion, & possible urinary retention
Benzamides	Sedation, headache, extrapyramidal reactions, and rare reports of tardive dyskinesia after proloned use

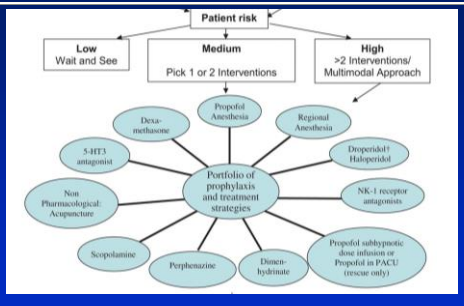
Adapted Annals of Pharmacotherapy. 2007; 41: 68

Sites of Action for Antiemetics



GSK PONV education series

PONV Prophylactic Agents



0 to 1 Low 2 Medium ≥ 3 High Risk

Anesth Analg. 2014;118

Adult PONV Prophylaxis

Medication	Dose	Timing
Aprepitant	40 mg PO	1 to 3 hours pre-op
Dexamethasone	4 to 5 mg IV (8 mg IV)	At induction
Dimenhydrinate	1 mg/kg IV	
Droperidol	0.625 to 1.25 mg IV	End of surgery
Ephedrine	0.5 mg/kg IM	
Haloperidol	0.5 to 2.0 mg IM or IV	
Methylprednisolone	40 mg IV	
Ondansetron	4 mg IV or 8 mg ODT	End of surgery
Palonosetron	0.075 mg IV	At induction
Promethazine	6.25 to 12.5 mg IV	
Ramosetron	0.3 mg IV	End of surgery
Scopolamine TDS	Transdermal patch	Night before or 2 hr before induction

PONV Prophylaxis in Children

Medication	Dose
Dexamethasone	150 mcg/kg up to 5 mg IV
Dimenhydrinate	0.5 mg/kg up to 25 mg IV
Droperidol	10 to 15 mcg/kg up to 1.25 mg IV
Ondansetron	50 to 100 mcg/kg up to 4 mg IV

5-HT_3 Agents

- Agents block serotonin receptors
  - 5 – HT 3 serotonin sites
  - peripheral serotonin receptors along GI tract
    - transmitted to CNS by way of vagus nerve
  - central serotonin receptors in CTZ
  - agents may act on the peripheral, central, or both to prevent PONV
    - unlike most antiemetics, it only acts at 1 receptor site
- Used for prevention and treatment of PONV

5-HT_3 Agents

- Most frequent side effects
  - headache, constipation, or diarrhea
- No sedation, dysphoria, or extrapyramidal effects
- Drugs are given at the end of the anesthetic
  - Package insert says the beginning of the case
- Ondansetron better for vomiting than nausea
  - same with all 1st generation 5-HT_3 agents
  - One study shows equal efficacy against both nausea & vomiting

Anaesthesia. 2009; 64: 147

5-HT_3 Agents

- Ondansetron 4 mg IV is the usual dose
  - 84% of all the 5-HT_3 agents: > 62 million patients
  - frequently effective as a single dose for 24 hours
- Dolasetron 12.5 mg IV is the usual dose
  - must 1st be converted to hydrodolasetron to be active, so there is a delay in onset
  - associated with prolonged QT interval, more so than any other 5-HT3 agent
- Granisetron 0.35 to 3.0 mg IV is the usual dose
- Tropisetron 2 mg IV is usual dose

5-HT_3 Agents Children

- Ondasetron (Zofran)
  - Approved for children 1 month and older
  - < 40 kg patient: 0.1 mg/kg to a maximum of 4 mg
  - > 40 kg patient: 4 mg adult dose
- Other 5-HT_3 agents little data in children
- Children with prolonged QT syndrome
  - be cautious with ondansetron & droperidol
    - not torsadogenic in healthy children but avoid in patients with prolonged QT sydrome

Anesth Analg. 2014;118

5-HT$_3$ Agents

- Drug interactions with SSRIs (fluoxetine)
  - SSRI causes an increased accumulation of serotonin
    - increase in 5 – HT could inhibit binding at 5-HT3 site
      - — decrease effectiveness of ondansetron
  - SSRI + Ondansetron = possible serotonin reaction
    - very rare
- Fentanyl + ondansetron + SSRI
  - possible serotonin reaction ------ very rare
- Repeat dosing < 6 hours for any 1st generation agent ineffective for PONV
  - Does work for CINV

Anesth Analg. 2007; 104(6): 1370

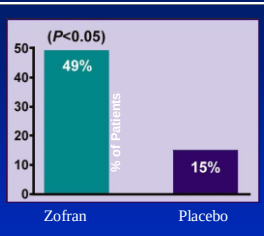
Comparison of 5-HT$_3$ Agents

	Ondansetron[1]	Dolasetron[2]	Granisetron[3]
Dose (mg)	4	12.5	0.1–1.0
Active Drug	Yes	No	Yes
Half-life (h)	3–5	6–8	5–8
Efficacy (%)	50–70	50–65	50–70

- Repeat ondansetron doses after 6 hours
- All have similar efficacy so use ondansetron as agent of choice

GSK 2006, Sanofi-aventis 2006, Roche 2005 data on file Medscape 2007

Zofran 24 Hour Efficacy in Preventing Further Episodes of PONV



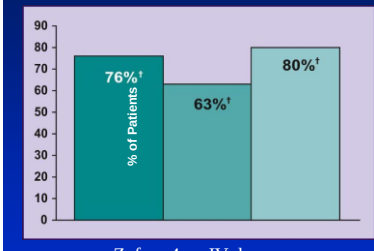
1. No prophylactic Antiemetics used
2. PACU patients with N/V got 4 mg ondansetron IV
3. 49% patients had no further PONV for next 24 hours

Outpatient surgery cases using nitrous oxide and opioids & single dose of ondansetron for PONV

Scuderi. Anesthesiology. 1993: 78; 815

Zofran Injectable 4mg Dose

3 separate studies showing ondansetron reduces incidence of PONV



1. No emesis for 24 hours with single dose of 4 mg

Anesthesiology. 1993: 78; 21 Anesth Analg. 1994: 79; 845 J Clin Anest 1996: 8; 644

Ondansetron – FDA Black Box

- FDA notice: 9/15/11
  - Ondansetron may increase the risk of a prolonged QT interval
    - may lead to Torsade de Pointes
  - Patients at risk include
    - congenital long QT syndrome
    - patients at risk for hypokalemia or hypomagnesemia
    - patients taking other medications that can lead to QT prolongation
  - FDA is requiring GlaxoSmithKline to conduct a study
    - determine the degree that Zofan may cause QT prolongation

Ondansetron – FDA Black Box

- Label warning in package insert
  - avoid use of ondansetron in patients with congenital long QT syndrome
- New labels will also include recommendations
  - ECG monitoring for hypokalemia & hypomangnesemia
  - CHF patients, bradydysrhythmias, & medications causing prolonged QT
- Personal opinion:
  - makes sense to keep magnesium in office
    - 1 to 2 grams IV

Ondansetron 2012

- GlaxoSmithKlein (GSK) study on ondansetron
  - Single 32 mg IV dose for CINV: no longer used
    - QT prolongation is dose dependent
  - IV dose 0.15 mg/kg IV Q 4 h up to 3 doses (CINV)
    - no single dose to exceed 16 mg IV
    - no change in PONV dose: 4 mg IV
    - no change in oral dosing of ondansetron
  - Correct K^+ & Mg^{++} prior to ondansetron use

FDA MedWatch: 6/29/12

Palonosetron (Aloxi)

- 2nd generation 5-HT_3 receptor antagonist
- Previous 5-HT_3 agents were competitive antagonists
  - competed with serotonin for receptor sites
- Palonosetron has allosteric binding at receptor sites
  - causes a conformational change at the receptor to increase the affinity of agent binding
  - binds more tightly & for a longer duration
  - 30 to 100X greater binding than ondansetron at the receptor site

Am J Health-Syst Pharm. 2009; 66(1): S11 Anesth Clinics. 2014;32:505

Palonosetron (Aloxi)

- Half life of drug is 40 hours
  - 4 to 10 times longer than the 1st generation agents
- Duration of action is now 0 to 72 hours
- Side effects are similar to ondansetron
  - headache 2%
  - constipation 4%
- Unlike the 1st generation agents
  - ***no Q-T prolongation***

Anesth Analg. 2008; 107: 439 Anesth Clinics. 2014;32:505

Palonosetron (Aloxi)

- Unlike 1st generation agents
  - ***lower incidence of nausea***
  - in study vs placebo: lower incidence of nausea for periods
    - 0 to 6 hrs., 6 to 72 hrs., and 0 to 72 hrs.
    - patients reported nausea to be mild to none
- Reduces nausea + vomiting
- Dose is 0.075 mg IV at start of the case
- No studies yet head to head against ondansetron
- Hospital Cost: $149.00 0.05 mg/ml 5 ml vial
  - manufacturer no longer makes smaller PONV vial
  - retail cost for same dose: $379.10 to $406.00

Anesth Analg. 2008; 107: 439-44

Ramosetron (Nasea)

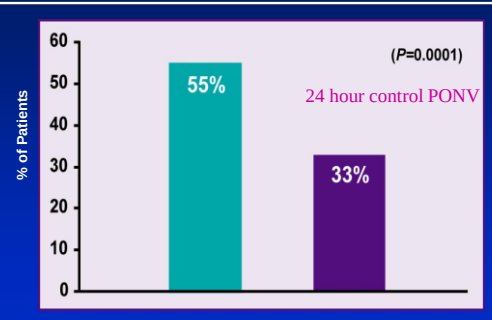
- 2nd generation agent developed in Japan
- 0.3 mg IV 30 mins before the end of surgery
- More effective than ondansetron 4 mg IV for PONV 2 to 48 hours
  - less vomiting and less need for rescue
  - was also found to be more effective for nausea than ondansetron
- Not currently available in United States

Anaesthesia. 2010; 65(5): 500-504

Ondansetron ODT

- Freeze dried ondansetron
- Dissolves on the tongue, no need for water
- Most frequent side effect is headache
- Absorbed by the GI tract – ***not by oral mucosa***
- ***Generic ODT is now available***
- 16 mg as two 8 mg ODT on the tongue 1 hour before surgery is prophylactic dose for PONV
  - No benefit to using the night before
  - Now that generic IV ondansetron is inexpensive, question the benefits of preop oral ondansetron
  - Has more of a post operative indication now

Ondansetron ODT 16 mg



GSK Data on File Ondansetron 16 mg ODT Placebo

Ondansetron ODT Side Effects

Adverse Event	ZOFRAN Tablets 16 mg (n=550)	Placebo (n=531)
Wound problems	152 (28%)	162 (31%)
Drowsiness/sedation	112 (20%)	122 (23%)
Headache	49 (9%)	27 (5%)
Hypoxia	49 (9%)	35 (7%)

Ondansetron ODT has no sedative effects

With the exception of headache, the reported side effects of Ondansetron are not statistically significant versus placebo

GSK data on file 2003

Ondansetron ODT & PDNV

- PDNV reduction with Ondansetron ODT
  - Few studies available for review
  - Gan et al: 8 mg BID for 1 day reduces PDNV
  - Hartsell et al: 8 mg BID for 3 days reduces PDNV
- Davis et al: outpatient T&A surgery children
  - Arrive at home 1st day: use 8 mg ODT
  - 8 mg ODT BID for 2 more days
  - Decrease PDNV in all cases, but less of an decrease if children needed emesis rescue while still in hospital
- No studies using ODT for rescue
  - ODT for rescue is an off label use according to GSK

Anesth Analg 2008; 106: 1117

Ondansetron & OINV

- Several studies that evaluated Ondansetron IV for OINV
  - 4 mg, 8 mg, 16 mg
- Majority of the studies showed
  - drugs were well tolerated
  - effectively reduced incidence of OINV
  - side effects similar to those for PONV
- GSK: injectable ondasetron for OINV is off label use
- No studies for Zofran ODT for management of OINV

Dexamethasone

- Prevent PONV and treat PONV
  - may use as a single rescue dose in 24 hours if none was used as prophylaxis
- Prophylactic dose of dexamethasone
  - adults: 4 to 5 mg IV after induction
    - 2014 guidelines: 8 mg IV after induction
  - children: 0.15 mg per kg – do not exceed 5 mg
  - found to be as effective as 4 mg ondansetron IV

Anesth Analg 2007; 105: 1615 Anesth Analg. 2014;118

Dexamethasone

- Side effects: GI upset, anxiety, & hyperglycemia
- Perineal Itch
  - acute perineal pain, irritation, burning, tingling, or itch
  - cause is unknown
  - lasts for 3 to 45 seconds
  - females > males
  - dilute in 50 ml. of fluid and give over 5 to 10 mins.
    - or wait until after induction
    - or add drug to IV bag

Anaesthesia. 2013; 68: 889

Dexamethasone

- What about the insulin dependent diabetic patient and using dexamethasone?
- Personal communication Apfel
  - 4 mg dexamethasone in stable IDDM not a problem
- Concern → acute, perioperative hyperglycemia
  - results in ↑ diuresis and possible hypovolemia
  - possible ↓ in immune function and wound healing
- 4 to 8 mg of dexamethasone does not cause significant hyperglycemia in healthy patients & stable DM
  - can be used for PONV prophylaxis

Anaesthesia. 2013; 68: 889 Anesth Analg. 2014; 118: 1204

Dexamethasone

- IDDM patients: avoid use of medrol dose packs
  - you are interfering with the patient's set insulin protocols – upsets the insulin balance that the endocrinologist established for the patient
- Unstable IDDM: dexamethasone is a relative contraindication
  - may see significant BS elevations for 6 to 12 hours
- Tumor Lysis Syndrome
  - hematologic tumors in children who received intraop decadron
  - rapid hyperkalemia, dysrhythmias, seizures, & cardiac arrest
  - do not use dexamethasone or any glucocorticoid

Anaesthesia. 2013;68:889 Anesth Analg. 2014;118: 85

Methylprednisolone

- Solumedrol 40 mg IV after induction
  - may substitute for dexamethasone for prophylaxis
- side effects similar to dexamethasone

Butyrophenones -- Droperidol

- Antidopaminergic D_2 agent that acts on CTZ
- O.625 mg or 1.25 mg at the end of the case
- Most effective dose 1.25 mg
  - more effective than ondansetron 4 mg
  - 0.625 mg equivalent to ondansetron 4 mg
- Children: 10 to 15 mics/kg if all other agents fail to work
  - use only as a rescue in children → not for prophylaxis
- FDA black box warning 2001
  - may prolong the Q-T interval
  - Torsades de points
  - Questions about 0.625 mg dose being the cause in few cases reported

Droperidol Revisited 2008

- At some institutions, new guidelines 2008
  - 0.625 to 1.25 mg IV
  - prophylaxis or rescue agent
  - no special testing needs to be done unless dictated by H&P
  - no special monitors needed
- What about the office???
  - do you feel safe using droperidol??
  - office is usually an isolated facility, you & the staff
    - Potential "blue alert" for using an antiemetic????
    - Personal preference: I will use another agent

Haloperidol

- Haloperidol for prophylaxis of PONV
  - 0.5 to 2 mg IV or IM
    - reduces risk of PONV
    - little to no sedation
    - dysrhythmias not reported
    - can cause Q-T prolongation: not a 1st line PONV agent
  - IV is not an FDA approved route of administration
  - Agent is not an FDA approved treatment for PONV
  - 1 mg IV is an alternative for droperidol 0.625 mg

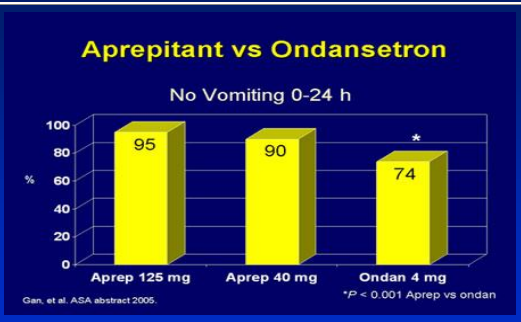
Aprepitant -- Emend

- Substance P is found in GI tract and throughout the CNS
  - relays noxious stimuli to brain – causes emesis
- NK_1 receptor antagonist – aprepitant (Emend) -- [emesis end]
  - highly selective brain penetrating antagonist
  - long half life: 40 hours
  - excellent efficacy against opioid induced emesis
  - *only single agent that can yield 90 to 95% emesis free patient*

Aprepitant

- Aprepitant
  - superior to ondansetron for emesis at 0-24 and 0-48 hrs.
  - delays the onset of 1st emesis better than ondansetron
  - aprepitant + dexamethasone better antiemetic than ondansetron + dexamethasone
- Dose is 40 mg PO 1 to 3 hours pre-op
  - give at least 1 hour before surgery
  - takes 2 to 3 hrs to reach peak effect
  - effective for 0 to 48 hours
  - less HA than ondansetron

Aprepitant -- Emend



Medscape Today 2007

Aprepitant -- Emend

- Decreased the effectiveness of BCP pills
  - recommend alternate birth control for ~ 1 month
  - may not be an issue with a single dose for PONV
    - still need to inform the patient
- Not a rescue agent for PONV
  - time of onset is too slow
- Not for use in children as yet
- Not very effective for nausea
  - consider adding TDS patch for nausea
- other NK-1 agents PO and IV will become available soon

Aprepitant -- Emend

- Cost to patient
  - > $50.00 for 1 dose
- 80 mg dose may be more effective than 40 mg PO
- Many hospitals do not stock
  - they feel it should be given prior to arrival at hospital
  - do ambulatory patients arrive less than 1 hr before surgery?
  - in ambulatory cases, who deals with PDNV, the anesthesiologist or the surgeon??
    - maybe we should be rethinking PDNV guidelines on these patients

Phenothiazines - Compazine

- Antidopaminergic D_2 agent that acts on the CTZ
- Prochlorperazine (Compazine)
  - most frequently used agent in this class
- Prophylactic and rescue agent
  - Prophylactic dose is 5 to 10 mg IV (at a rate of 5 mg per min.) 15 to 30 mins prior to end of surgery
    - IV use may cause hypotension & sedation especially in the elderly
  - Rescue agent 5 to 10 mg IV or IM
    - may repeat 2.5 to 10 mg IV or IM Q 4 h
    - oral dose of 5 to 15 mg can be tried instead of IV
- Has moderate histamine site activity H 1

Phenothiazines - Compazine

- Extrapyramidal effects with Compazine
- Torticollis --- contracture of cervical neck muscles to twist head and neck
  - eye movements
  - protrusion of tongue
  - smacking of lips
- Sedation and lethargy post op
- Adult PDNV can use 25 mg suppository BID
- Children: IM dose 0.1 to 0.15 mg per kg
  - these agents also sedate - risk in children
  - check with pharmacist about suppository dose

Phenothiazines - Promethazine

- Promethazine (Phenergan)
- ***Has most of its effect on Histamine H1 site***
- Unlike Compazine, give prophylactic drug at the start of the case
  - 6.25 mg to 12.5 mg IV
- Rescue agent drug use
  - 12.5 mg IM or IV Q 4 h prn
- Very popular antiemetic in dental anesthesia
  - Inexpensive & effective
  - Long history of use in office anesthesia

Phenothiazines - Promethazine

- Side effects: sedation, extrapyramidal, akathisias (restlessness, jittery), hypotension
  - Similar effects as prochlorperazine
- Serious adverse reports on the use of promethazine IV
  - extensive tissue injuries and amputations from inadvertent arterial injections & IV extravasations
  - Some are calling for the FDA to ban its use IV and just go to deep IM or PO use
  - **Must have a secure and running IV before you consider using this drug**

Phenothiazines - Promethazine

- Promethazine for injection
  - Contains phenol – a tissue irritant
  - pH is 4.0 to 5.5
    - low pH makes it corrosive
- Multiple case reports in nursing & pharmacy literature about adverse side effects
  - Sheth et al. 2005 reported that the incident rate ratio for promethazine is higher than all other antiemetics combined
  - Rates were higher if the patient is older than 65

Sheth. Ann Pharmacother. 2005; 39: 255-61

Phenothiazines - Promethazine

- IV injections adverse side effects
  - severe burning and arm pain
  - erythema, swelling, vessel spasm, phlebitis
  - nerve injuries, arm paralysis, tissue necrosis, & gangrene
- Drug is caustic to the intima of blood vessels
  - extravasation damages tissue and nerves
  - worst damage is inadvertent intra-arterial injections
- Surgical interventions include
  - fasciotomy, skin grafts, & amputations

Phenothiazines - Promethazine

FIGURE 2: Ischemia led to necrosis of all digits.

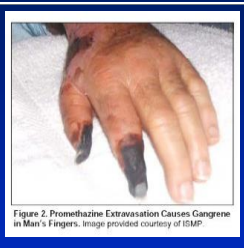


Figure 2. Promethazine Extravasation Causes Gangrene in Man's Fingers. Image provided courtesy of ISMP.

- Supreme court case: Wyeth v Levine
- Ms Levine, a musician, had promethazine extravasation which lead to an arm amputation
- Successful litigation against her physician and then she sued the drug company over improper drug labeling. The court upheld a $ 6.7 million award against Wyeth

Phenothiazines - Promethazine

- Recommendations for use
  - Concentration no greater than 25 mg/ml
  - Dilute the drug in 10 to 20 mls of fluid
  - Limit the dose initially to 6.25 mg to 12.5 mg
  - Give over at least one min – consider over 10 mins
  - Remain with the patient during the entire injection
  - No hand or wrist veins --- avoid the ACF to prevent the drug from damaging arteries, veins, & nerves
  - Use the back of the arm or a central line if present
  - Inject in IV administration port farthest from the pt. and make sure the IV is freely running
  - Have the patient report any pain or swelling

Guidelines - Promethazine

- Patients < 65 y.o.
  - Dispense promethazine only at 12.5 mg total dose
- Patients > 65 y.o. – if order promethazine
  - Substitute Zofran 4 mg IV as single dose
  - Substitute Zofran 4 mg IV Q 6 hrs if mutiple dosing is needed -- CINV (chemotherapy)
- Patients > 65 y.o. – if order prochlorperazine
  - Substitute Zofran 4 mg IV as single dose
  - Substitute Zofran 4 mg IV Q 6 hrs mutiple dosing
- Dilute phenergan 12.5 mg in 10 ml NSS and inject over 3 to 5 mins.

Phenergan & Compazine

- Lessons learned
  - Do not use either in patients over 65
    - high incidence of extrapyramidal symptoms
  - Avoid Phenergan in pediatric and adult population for PONV
    - Pediatric patients: respiratory depression " black box"
      - None for patients < 2 yrs old
    - Still a risk respiratory depression in children > 2 yrs old
  - Other effective antiemetic agents without these side effects
    - Ondansetron is obvious choice

Benzamide -- Metoclopramide

- Metoclopramide (Reglan)
- Antidopaminergic D_2 agent
  - acts on peripheral GI tract receptors and central receptors in the CTZ
  - has weak 5-HT_3 activity at high doses
- Prophylactic & rescue agent
  - dose is 10 mg IV Q 4-6 hours prn
    - *reported to be ~ 50% effective at that dose*
    - *not recommended by consensus panel 2007 at that dose*
  - dose of 25 to 50 mg IV
    - effective for PONV for 0 to 24 hours

ASA Refresher Course. 2008; 36(1): 1-10 Br J Med. 2006; 333: 324

Benzamide -- Metoclopramide

- Prokinetic agent
  - increases gastric emptying
  - GERDS patients: less risk of regurgitation & aspiration by emptying the stomach
- Black box FDA
  - tardive dyskinesia, an irreversible disease
  - < 1% risk of occurrence with chronic use of the drug
- Other agents have replaced metoclopramide as a 1st line drug

Benzamide -- Tigan

- Trimethobenzamide (Tigan)
- Antidopaminergic D_2 agent
  - also has histamine blocking activity
- Tigan suppositories in children and adults
  - *FDA says they are ineffective*
- Routes for Tigan: PO or IM
  - children & infants: only use PO route of administration
  - adults: 200 mg IM 3 to 4 times a day prn
- Rescue drug only
  - no longer a first line agent

Anticholinergics - Transdermal Scopolamine Patch

- Transdermal scopolamine patch (TDS)
  - 1.5 mg patch
    - delivers loading dose & 1.0 mg over 3 days
- Anticholinergic – antimuscarinic agent
  - blocks vestibular transmissions to CNS
    - used for motion sickness
  - blocks histaminic sites in the CTZ
- Apply patch the night before
  - no less than: 2 hours before anesthesia

J. Clin Anesthesia. 2012; 24: 334

Anticholinergics - Transdermal Scopolamine Patch

- Not a rescue agent
  - too long an onset of action
- Better for nausea than vomiting
- Not for children

Anticholinergics - Transdermal Scopolamine Patch

- Studies comparing TDS to droperidol 1.25 mg & ondansetron 4 mg
  - similar reduction in PONV and need for rescue over 0 to 72 hrs
  - more effective when used in mutimodal therapy
- Most common side effects
  - dry mouth, blurred vision, & dizziness
  - confusion as a side effect is not supported by literature
  - urinary retention especially the elderly

J Clin Anesth 2009; 21(4) Curr Opin Anaesthesiol. 2009; 22: 532

Propofol

- Propofol has antiemetic properties
  - possibly works on serotonin sites
- General anesthesia: see decrease in PONV
- Prophylactic antiemetic in addition to being the anesthetic agent: prophylactic doses
  - Sub hypnotic infusion during the case 1 mg/kg/hr did decrease retching & PONV
  - Hypnotic doses by observation decrease PONV
- Rescue dose: 20 mg IV in adults

Borgeat. Anesth Analg. 1992: 74; 539

Propofol

- Fujii. JOMS. 2002: 60; 1246
  - gave 0.5 mg per kg at the end of surgery
  - see delay in emergence from anesthetic
- Results 0 to 3 hours
  - Emesis free 90%
  - Nausea 7%
  - Vomiting 7%
- Results 3 to 24 hours
  - Emesis free 87%
  - Nausea 10%
  - Vomiting 7%

Propofol

- Third molar case study
  - Propofol induction; sevoflurane maintenance
- Antiemetic agents studied
  - Propofol 0.5 mg/kg IV at end of case
  - Propofol 0.5 mg/kg + Dexamethasone 8 mg at end of case
- PONV monitored for 0 to 24 hrs
  - Placebo: 16 pts with PONV
  - Propofol: 8 pts with PONV
  - Propofol + dexamethasone: 2 pts with PONV
- Propofol – Dexamethasone combination was more effective than the single agent
  - dexamethasone was likely the cause of longer effectiveness

Br. J. OMFS. 2008; 46: 207

Midazolam as Antiemetic

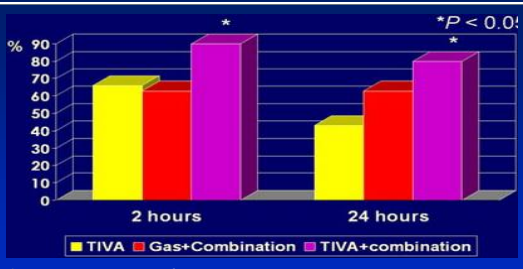
- Midazolam has been shown to
  - reduce nausea post operatively
  - slight decrease in vomiting post operatively
  - may last up to 24 hours
- Acts on the higher centers of the brain
- not very effective as single agent antiemetic
  - 2 mg IV at end of case

J. Clin. Anesthesia 2004: 16; 177

Multiple Agents Reduce Incidence

- Reductions seen with various agents:
  - Zofran 26%, Decadron 26%, Droperidol 26%, Propofol 19%, Remifentanil not significant
- If patients baseline was 50% risk of PONV and you add one or more agents, see the following reduction in PONV
  - 1 agent reduces PONV to ~ 40% risk
  - 2 agents reduce PONV to ~ 30% risk
  - 3 agents reduce PONV to ~ 20% risk
  - Levels out at about 10% no matter how many agents are used

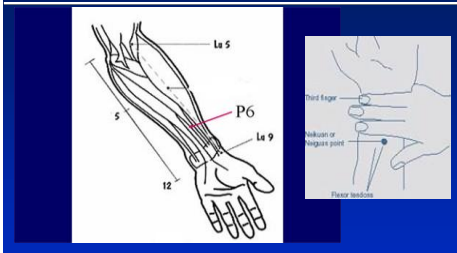
Propofol + Antiemetics



- TIVA only used propofol, no antiemetics
- Gas + Zofran + Decadron
- TIVA + Zofran + Decadron

Gan. Anest Analg 2003 Medscape Today 2007

Accupuncture



- Similar to ondansetron for vomiting
- Better than ondansetron for nausea
- P6 point is 4 cm proximal from the wrist crease

Gan. Anesth Analg. 2004: 99; 1070

Ginger

- Traditional Chinese herbal medicine
- 6-Ginerol is the active agent
- Has been used for motion sickness
- Studies 1 to 5 grams given preoperatively are inconclusive for PON (nausea – not vomiting)
- " Mother's remedy" 8 oz of flat, real ginger ale
  - 1 gm of ginger in 8 oz
  - 1 gm of ginger has shown some nausea relief
    - No harm but possible benefit
- 2012 Guidelines: not effective

Am J Obstet Gynecol. 2006; 194:95 Br J. Anest. 2000; 84: 367

Aromotherapy for Nausea

- Essential oil of ginger
- Essential oil of ginger, spearmint, & cardamom
- Inhale through nose & exhale through mouth
  - Dose = 3 inhalations in a row
  - Reevaluate in 5 min
    - if still has nausea or patient vomits
      - — administer IV antiemetic drug
- Rate of PON (nausea) was reduced
  - reduced the number of requests for antiemetic rescue

Hunt. Anesth Analg. 2012. Aromotherapy

Aromotherapy for Nausea

- isoprophyl alcohol inhalation
  - ineffective for PONV prophylaxis
  - once nausea develops
    - effective relief
    - more rapid relief than ondansetron or promethazine
    - Anesth Analg. 2014; 118

Cannabinoids

- Active constituents of cannibus (marijuana)
- Nabilone & tetra-hydrocannabinol
  - effective for CINV
  - ineffective for PONV
- Side effects:
  - "feeling high", depression, sedation, euphoria, paranoia, hallucinations.
- *"dental office pot emee-free" "DOPE"*
  - when legalized may study PO marijuana for PONV

Costs of Antiemetics

- Promethazine: the old standard
  - 25 mg/ml 1 ml $ 2.50
- Tigan
  - 100 mg/ml 2 ml $ 8.50
- Dexamethasone
  - 4 mg/ml 30 ml $21.00
- Zofran generic
  - 4mg IV dose $ 9.00 for 5 doses
- Zofran ODT 8mg (Brand name)
  - 6 pills (1 pill BID) $ 127.99

Costs of Antiemetics

Drug	#1	#2	#3
Aprepitant 40 mg			
1 dose	$85.35	$50.66	$55.24
2 doses	$162.55	$96.32	$108.80
Ondansetron 8mg ODT			
3 doses	$12.00	$6.64	$102.41
5 doses	$12.00	$7.73	$161.60
TDS patch			
1 patch	$13.99	$13.96	$15.29
Compazine Suppositories 25 mg			
2 doses	$11.00	$6.78	$9.35
4 doses	$21.00	$8.57	$18.70

Aprepitant (Emend) is still cheaper than treatment in the ER.

Suggested Office Protocol

- Assess each patient's risk for nausea & vomiting
- Patients with no nausea & vomiting in the office
  - ~ 50% of those patients will develop PDNV at home
  - overall incidence of PDNV = 37.1%
- High risk patients (3 or more risk factors)
  - less PDNV over 0 to 3 days if use 3 or more anti emetics vs a single agent

Curr Opin Anaesthesiol. 2009; 22: 532 Anesth Analg. 2008; 107: 452-8

Suggested Office Protocol

- Consider more liberal use of antiemetics for office surgery
  - discharged patients have less access to the doctor
  - doctor has limited treatment options for rescue agents at home
- Remember: nausea is more common than vomiting
  - moderate to severe nausea is just as distressful as vomiting

Suggested Office Protocol

- Patients with a low risk of PONV
  - propofol + dexamethasone
    - primary role of agents = anesthesia & surgery
- Patients with a past history of PONV
  - propofol + dexamethasone for the anesthesia
  - consider a third agent
    - ondansetron 4 mg IV at end of the case would be the first choice
    - 3rd agent as per surgeon or anesthesiologist

Suggested Office Protocol

- Multiple risk factors for PONV or patient anxiety about PONV
- Option #1
  - TIVA anesthesia with propofol + midazolam
    - avoid volatile gas anesthetics and nitrous oxide
  - Dexamethasone 8 mg IV at induction
  - Ondansetron 4 mg IV at end of the case
    - at least 15 minutes before end of case
  - Consider 4th agent with longer duration
    - TDS patch or aprepitant (Emend)

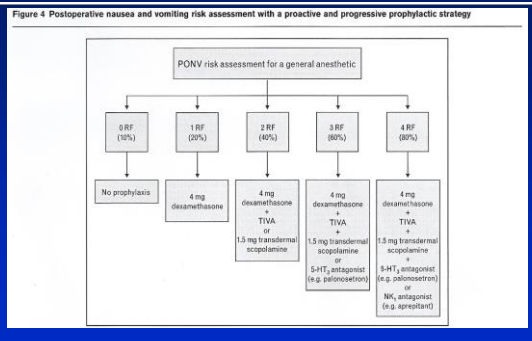
Option # 1

- Other alternatives for 4th antiemetic agent
  - prochlorperazine (Compazine)
    - 5 to 10 mg IV at the end of case
  - diphenhydramine (Benadryl)
    - 10 to 50 mg IV
  - dimenhydrinate (Dramamine)
    - 1 mg/kg IV
  - atropine instead of glycopyrrolate at start of the case
    - 0.4 mg IV
  - ondansetron ODT 8 mg tablets
    - 1st dose as soon as get home then at HS
    - BID dosing to follow for next 1 to 2 days

Suggested Office Protocol

- Patients with a history of severe nausea and vomiting especially when using opioids
- Follow steps of Option #1
  - Propofol, midazolam, dexamethasone, & ondansetron
  - Best option for the 4th agent would be aprepitant
    - Very effective for opioid induced nausea & vomiting (OINV)
    - need to give it 1 to 3 hours preoperatively
    - dose is 40 mg PO
    - biggest concern using aprepitant is just the cost
- Ondansetron is useful with narcotics
  - may have effect of mu receptors

Treatment Protocol Option # 2



Curr Opin Anaesthesiol. 2009; 22: 532-538

Treatment Protocol Option # 2

- Eliminate the use of ondasetron 4 mg IV
- More use of the TDS patch
- Palonosetron is their preferred 5-HT_3 agent
  - If you used ondansetron intra-op, the addition of another 5-HT_3 agent within 6 hours has no benefit for PONV
  - Palonosetron has longer duration 48 to 72 hours
- Aprepitant also recommended 40 mg PO
  - again, the incorporation of longer acting agents
- Remember, this was a study on ambulatory PDNV

2014 Guidelines for Prophylaxis

- Low risk patient & medium risk patients
  - no treatment or dexamethasone 4 mg
  - consider ondansetron 4 mg or TIVA
- High risk patient
  - dexamethasone 4 mg + ondansetron 4 mg + TIVA
  - consider other agents case by case basis
    - droperidol 1 mg in adults
    - dimenhydrinate 1 mg/kg IV
- Doses in Children
  - dexamethasone 0.15 mg/kg
  - droperidol 10 to 15 mcg/kg
  - ondansetron 0.1 mg/kg
  - dimenhydrinate 0.5 to 1.0 mg/kg

Anesth Analg. 2014;118: 85

Rescue Treatment in Office

- No prophylaxis: use Ondansetron 4 mg IV
- Ondansetron < 6 hours: use different drug
- Ondansetron + other agents < 6 hours: use different agent for rescue
- Ondansetron +/- other agents > 6 hours: give Ondansetron
  - do not repeat Dexamethasone in 1st 24 hours: little to no effect
  - do not use scopolamine – takes too long to be effective
  - can not use emend as a rescue agent
- Studies in CINV have shown if one 5-HT3 agent fails, you can use another 5-HT3 & get results
  - not shown to work for PONV or PDNV

PDNV at Home

- Oral agents????
  - if have vomiting, how do you keep these pills down?
- Tigan suppositories: ineffective in children and adults
- Compazine suppositories:
  - adults 25 mg BID
  - elderly 12.5 mg BID
  - children: call pharmacist for current dosing
- Phenergan suppositories:
  - adults 12.5 to 25 mg Q 4 to 6 h as needed
  - elderly 12.5 mg Q 4 to 6 h as needed

PDNV at Home

- Phenergan suppositories for children
  - none if child < 2 yrs old: risk of fatal respiratory depression
  - children > 2 yrs old: still a risk of respiratory depression ---- 0.5 mg per pound with a maximum of 25 mg Q 4 to 6 h --- call pharmacist
  - consider another drug for children especially if post anesthesia
  - rectal doses: do not see the same injuries as with the IV route
- Emend & scopolamine patches
  - not rescue agents & they are not used for children

PDNV at Home

- Ondansetron ODT for PDNV
  - doses used are 8 mg BID for 1 to 3 days prn
- Ondansetron ODT for OINV
  - Doses used are 8 mg BID for 1 to 3 days prn
- All off label uses for ondansetron ODT
- Success of prophylaxis is better than rescue for just about every agent
  - same holds true for ondansetron ODT
  - patient may not respond to ODT

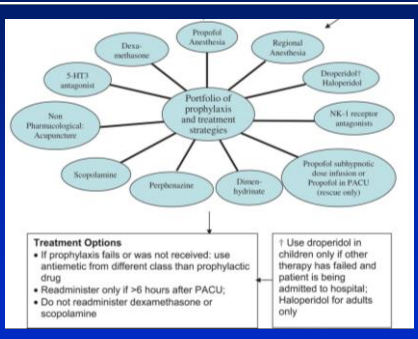
PDNV at Home

- Prolonged, severe episodes of PDNV
  - not relieved by medications you prescribed in office
  - not relieved by additional medications you called in
  - patient & family unhappy with the current events
    - they want relief & want it now
- Options
  - meet them after hours at the office?
    - rehydrate with IV fluids
    - what additional antiemetics do you stock in the office?

PDNV in ER

- Send them to the ER or meet them there
  - IV fluids & IV analgesics for discomfort
  - Antiemetics agents from a different class
  - Monitor progress over a couple of hours
  - if nausea & vomiting persists
    - 12 lead ECG, cardiac history, syncopal history
    - consult with ER physician
    - droperidol 0.625 mg IV

2014 Guidelines for Rescue



2014 Guidelines for Rescue

- Patients received dexamethasone 4 mg IV + ondansetron 4 mg IV as prophylaxis
  - use droperidol 1 mg IV
  - use dimenhydrinate 1 mg/kg IV
  - haloperidol is for adults only
- Children
  - use droperidol only if other therapies have failed and patient is being admitted to hospital

Points to Remember

- Nausea is more common than vomiting
  - mild – moderate – severe nausea is just as distressing to a patient as vomiting
- Patients with Apfel risk scores **> 3**
  - high risk for PONV
- Antiemetics commonly given both at the start and end of surgery
- Prevention of PONV is more successful than rescue treatment

Points to Remember

- Office Surgery
  - ~ 35 million outpatient surgical cases each year
    - 33% have general anesthesia
    - PDNV rate = 37.1%
      - — 4.3 million patients suffer from PDNV
  - ambulatory patients who experience N/V in PACU
    - have 3 fold increase in PDNV
  - incidence of PDNV is underestimated because of the low incidence in PACU & poor discharge follow up

Apfel et al. 2012

Points to Remember

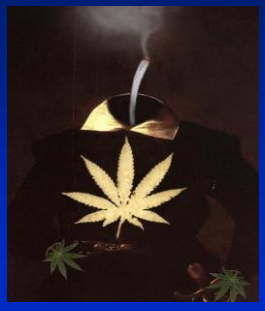
- TIVA is not a substitute for antiemetic drugs
  - may be effective in recovery but is too short acting for discharge N/V
- Ondansetron has a plasma half life of ~ 3 hrs
  - Safe to assume a single IV intraoperative dose will be ineffective for PDNV
- Glucocorticoids will not decrease risk in PACU
  - do decrease risk on discharge

Apfel et al. 2012

Points to Remember

- More likely to experience N/V after leave office
- Aprepitant, palonosetron, & TDS patch
  - longer duration agents
  - excellent options for outpatient surgery since patients do not have immediate access to rescue
  - aprepitant for opioid nausea & vomiting
- Ondansetron ODT
  - useful as prophylactic agent for discharged patients

If all else fails…….

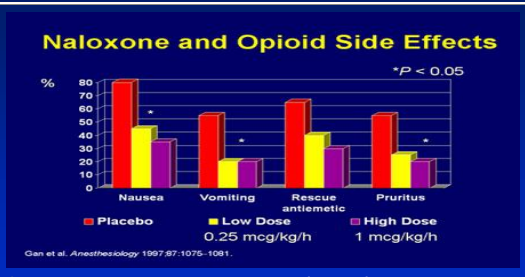


Forget the pharmacy. The patient will need to seek care from an ***"alternative health care provider".*** We hope you don't have a name or phone number to give out.

Thank you for your kind attention

Edward C. Adlesic, DMD
Oral and Maxillofacial Surgeon
Pittsburgh, Pa
edward_adlesic@msn.com

Low Dose Narcan & PONV



- 1 amp Narcan = 400 mics: dilute in 1 liter fluid: infuse over 24 hours
- Will not decrease analgesia, but decreases N/V, need for rescue agents, and the incidence of pruritus 0.25 mics/kg/hour

Medscape Today 2007

Koivuranta Risk Score

Risk factor	Points	N	V
0 risks	0 points	17%	7%
Female	1	18%	7%
Sx > 60 mins	2	42%	17%
Non smoker	3	54%	25%
Motion sickness	4	47%	38%
PONV history	5	87%	61%

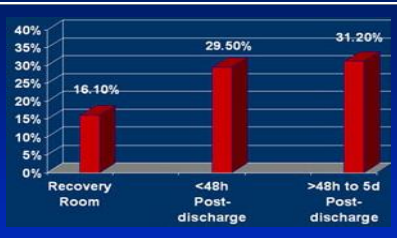
- Another risk system to evaluate adults
- Does not associate perioperative narcotics as a risk factor

Category	Definitions	Examples
Neurosurgery	All intracranial and open spine procedures.	Neurosurgery procedures: Ommaya reservoir, shunts, brain biopsies, trans-sphenoidal procedures. Spine procedures.
Head and neck	All head and neck procedures.	All procedures involving the head and neck, intraoral, ophthalmologic, major neck dissections, all wide local excisions, and nasal endoscopic procedures.
Thoracic	All intrathoracic procedures.	Any open or videoscopic procedures involving the chest cavity such as thoracotomy, median sternotomy, thoracoscopy, and mediastinoscopy.
Abdominal	All intraabdominal, pelvic, and retropelvic procedures.	Any open or laparoscopic procedure in the abdomen or pelvis, including umbilical, ventral, or abdominal incisional hernias. If a procedure involved both thoracic and upper abdominal area (such as esophagectomies) it was classified as abdominal.
Endoscopic	Intrauterine, vaginal, prostate, bladder, colon, stomach, and lungs.	All endoscopies including: hysteroscopy, tandem, and ovoids, vaginal, prostate: ablations and brachytherapy, cystoscopy, colonoscopy, esophagogastroscopy, and bronchoscopy.
Breast or axilla	All breast and/or axillary procedures.	Any breast or reconstructive breast (procedures following mastectomy were included). All axillary dissections and sentinel node biopsies involving the axilla.
IMS	All puncture procedures and procedures of the skin or muscles of the extremities, trunk, perineum and inguinal hernias and groin dissections.	Puncture procedures: CVC placement, bone marrow biopsies, and lumbar punctures. Procedures of the skin or muscles such as wide local excisions on the extremities or trunk, arms, legs, back, or abdominal wall. Male genitalia (including orchiectomy, circumcision, penectomy), vulvectomies, and groin procedures, including inguinal hernias. Orthopedic procedures.

IMS = integumentary-musculoskeletal and superficial category; CVC = central venous catheter.

Anesth Analg. 2010; 110: 403-9

PDNV (Post discharge N/V)



- PDNV: few published reports
- Patients who developed PDNV: only 16% had N/V in the PACU (office)
- 24 hours after surgery: the incidence of nausea is greater than vomiting
  Nausea = 35.70% Vomiting = 19.60%

Anesth Analg. 1995: 80; 903 Anesthesiology. 2003: 99; 488 Medscape Today 2007

Apfel Risk Score

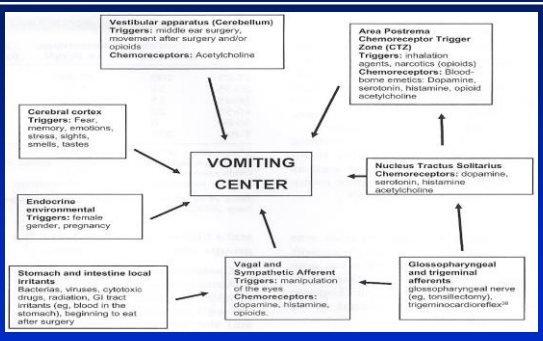
Female	1 point
History PONV or motion sickness	1 point
Non smoker	1 point
Perioperative opioids	1 point
No risks for PONV	10% risk N/V
1 risk	21%
2 risks	39%
3 risks	61%
4 risks	79%

- Good risk evaluation for adults

Phenothiazines

- Neuroleptic malignant syndroms NMS
  - occur in any patient using phenothiazines
  - hyperthermia, severe extrapyramidal dysfunction
  - alterations in consciousness, altered mental status
  - sinus tachycardia, hypertension or hypotension
  - diaphoresis and acute renal failure
  - death has occured

Regulation of Vomiting



Silva et al. JOMS. 2006; 64: 1385

Aprepitant (Emend)

- Substance P
  - afferent neurotransmitter for emesis
  - peripheral sites in stomach & intestine can release substance P
  - central sites in the brain that react to substance P
  - 2 important CNS areas are
    - CTZ receptor sites
    - area between the medial nucleus tractus solitarius & VC
  - receptor sites are the neurokinin – 1 sites
    - NK - 1

Neurokinin (NK-1) Antagonists

- Aprepitant (Emend) --- "emesis end"
  - prevents both the acute and delayed phase of vomiting
    - 5-HT_3 antagonists usually only work on the acute phase
  - highly selective brain penetrating antagonist
  - long half life 9 to 12 hours
  - excellent efficacy against opioid induced emesis
  - ***only available single agent that can yield 90 to 95% emesis free patients***
  - superior to ondansetron for no emesis 0 to 24 hrs.
    - even better during the next 24 to 48 hrs
  - delays the onset of 1st emesis better than ondansetron

Aprepitant -- Emend

- Augmented the activity of 5-HT3 agents and dexamethasone for N/V in CINV patients
- Less headache than ondansetron
- Dose is 40 mg PO 1 to 3 hours pre-op
  - give at least 1 hour before surgery
  - takes 2 to 3 hrs to reach peak effect
- Not a rescue agent for PONV
- Not for use in children as yet

Neurokinin (NK-1) Antagonists

- Decreased the effectiveness of BCP pills
  - recommend alternate birth control for ~ 1 month
  - may not be an issue with a single dose but why take the risk at this point
- In CINV where used doses over 3 days
  - coumadin was less effective
  - INR levels dropped down
- Do not use Emend if currently take
  - cisapride (Propulsid)
  - pimozide (Orap)
  - terfenadine (Seldane)
  - astemizole (Hismanal)
  - aprepitant raises their serum levels to toxic plasma levels
  - aprepitant is weak to moderate CYP3A4 inhibitor

Neurokinin (NK-1) Antagonists

- Aprepitant 40 mg single oral dose vs IV agents ondasetron + dexamethasone + third agent
  - third agent
    - metoclopramide 10 mg IV
    - diphenhydramine 25 mg IV
    - compazine 5 mg IV
- 3 combinations were given Q 6 h for 48 hrs
  - aprepitant was a single 40 mg PO dose
- Less PONV with single aprepitant vs the 3 combinations given over 48 hrs
  - still had a few episodes of emesis – not totally eliminated
  - study suggested combining aprepitant with at least 1 other agent to try and get complete emesis free period for 48 hrs

Hartrick et al. Pain Practice. 2010; 10(3): 245

Neurokinin (NK-1) Antagonists

- Aprepitant as single PO dose + combination therapy of 1 to 2 other agents
  - less PONV & PDNV with the combination therapy than just aprepitant alone
  - Scientific World Journal 2009; 28(9): 291
- This seems to be a very reasonable technique for office surgery in patients with a high risk of PDNV
  - get 48 hours of decreased nausea & vomiting while still using postoperative narcotics for pain

Neurokinin (NK-1) Antagonists

- Aprepitant 40 mg PO is approved for PONV
  - prophylactic agent only
  - not for rescue
  - not for children
- Fosaprepitant is the IV form of the drug
  - only approved for CINV at present
- Casopitant
  - new NK-1 agent in phase III studies