New and Emerging Therapies for Preventing Postoperative Nausea and Vomiting

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New and Emerging Therapies for Preventing Postoperative Nausea and Vomiting

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New and Emerging Therapies for Preventing Postoperative Nausea and Vomiting

PROGRAM AGENDA

Introductory Remarks
Tricia Meyer, M.S., Pharm.D., FASHP, Program Moderator

Using Evidence-based Consensus Guidelines and Risk Stratification Tools to Prevent and Manage PONV
Tricia Meyer, M.S., Pharm.D., FASHP

Current and Emerging Therapeutic Options for Prevention of PONV: Developing Strategies for Optimal Outcomes
Julie Golembiewski, Pharm.D.

PROGRAM FACULTY

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New and Emerging Therapies for Preventing Postoperative Nausea and Vomiting

**PROGRAM DESCRIPTION**

Postoperative nausea and vomiting (PONV) occur in 25-30% of surgical patients despite the advances in options for managing PONV in recent years. Consensus guidelines for preventing and managing PONV released by an international panel of experts in 2006 facilitate the development of patient-specific plans of care for prevention and treatment of PONV. Several new pharmacological agents are in development, and new evidence is expected to support the use of drugs currently used to manage chemotherapy-induced nausea and vomiting in the prevention of PONV. Based on the current gap in best practices in selecting appropriate antiemetic therapy and the anticipated increase in the number of pharmacological options for managing PONV, the role of the pharmacist is particularly important in the selection of appropriate drug therapy for prevention and management of PONV.

This program will describe the prevalence of and risk factors for PONV and current consensus guidelines for preventing and managing PONV. The efficacy and safety profiles of current and emerging drug therapies for prevention of PONV also will be addressed. The program will conclude with a discussion of the role of the pharmacist in developing strategies to implement evidence-based recommendations for the prevention and treatment of PONV in patients undergoing surgical procedures.

**LEARNING OBJECTIVES**

At the conclusion of this presentation, participants should be able to:

- Discuss the prevalence of and risk factors for PONV.
- Describe current consensus guidelines for the prevention and management of PONV.
- Compare and contrast the efficacy and safety profiles of current and emerging drug therapies for prevention of PONV.
- Explain the role of the pharmacist in developing strategies to implement evidence-based recommendations for the prevention and treatment of PONV in patients undergoing surgical procedures.
Tricia Meyer, M.S., Pharm.D., FASHP, is Director of Pharmacy Services at Scott & White Memorial Hospital, in Temple, Texas and an Assistant Professor in the Department of Anesthesiology for Texas A&M University, College of Medicine. Dr. Meyer’s main focus is on pharmacy operations, which includes administrative responsibilities for central dispensing, sterile preparations, perioperative pharmacy satellite, pediatric pharmacy satellite, long-term-care facility pharmacy, investigational drug service, home care infusion service, general and children’s clinic retail pharmacies, and a pharmacist-run community internal medicine medication management service. Her role as Assistant Professor in Anesthesiology includes research, publications, development of practice parameters, teaching, and cost-saving initiatives.

Dr. Meyer has served in various offices and committees in state and local pharmacy associations, in addition to being a member on the Pharmacy and Therapeutics Committee, Institutional Review Committee, Complimentary/Alternative Medicine Interest Group, Recognition Committee, Anesthesiology Research Oversight Committee, and numerous other committees within Scott & White. She also serves on the committee for education and training for Anesthesia Patient Safety Foundation. Dr. Meyer received the Scott & White Quality Award in 1998, Abbott National Hospital Pharmacy Award in 1997, 1998, and 1999, and the Organon Leadership Award in 1998. She is a Fellow of the American Society of Health-System Pharmacists.
New and Emerging Therapies for Preventing Postoperative Nausea and Vomiting

41st ASHP Midyear Clinical Meeting
Anaheim ~ Orange County, California

Using Evidence-based Consensus Guidelines and Risk Stratification Tools to Prevent and Manage PONV

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Temple, Texas

The Dilemma in the Decision Making for PONV Therapy

- Antiemetics are a top expenditure
- Highly marketed/promoted class of drug (5-HT-3 receptor antagonists alone represent a billion $ market)
- Antiemetic use is throughout system
- Antiemetic shortages/Black Box warning
- Lack of evidence in some areas
- Wide variations in prescribing and utilization of antiemetics
- Overwhelming amount of publications
The Dilemma in the Decision Making for PONV Therapy

- Literature and information confusing, conflicting, complex
- Newer agents are being developed and studied
- Considerable gap between obtaining results in trials and implementing in practice
- Limited guidelines available
- Need for an “easy” guide for the front line practitioners
- Patient preferences or requests

Incidence of PONV

- Postoperative nausea and vomiting occur in 25-30% of surgical patients
- Nausea rates range from 22 to 38%
- Vomiting occurs less frequently at a rate of 12-26%
- In certain patient populations the rate can approach 70%

1 Watcha et al. Anesthesiology 1992;77:162-84
4 Carroll et al. Anesth Analg 1995;80:3

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

- Nearly 65% of patients did not experience PONV symptoms until after discharge from the PACU.

* PACU=Postanesthesia care unit.
PONV: An Undesirable Consequence of Surgery

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

<table>
<thead>
<tr>
<th>Rank</th>
<th>Preoperative Anesthesia Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vomiting</td>
</tr>
<tr>
<td>2</td>
<td>Gagging on endotracheal tube</td>
</tr>
<tr>
<td>3</td>
<td>Incisional pain</td>
</tr>
<tr>
<td>4</td>
<td>Nausea</td>
</tr>
<tr>
<td>5</td>
<td>Recall without pain</td>
</tr>
<tr>
<td>6</td>
<td>Residual weakness</td>
</tr>
<tr>
<td>7</td>
<td>Shivering</td>
</tr>
<tr>
<td>8</td>
<td>Sore throat</td>
</tr>
<tr>
<td>9</td>
<td>Somnolence</td>
</tr>
</tbody>
</table>

Postoperative Anesthesia Outcomes

Adapted from Macario A et al. Which clinical anesthesia outcomes are important to avoid? The perspective of patients. Anesth Analg. 1999;89:652–658. © 1999. With permission from Lippincott Williams & Wilkins.

Assessing a Tool to Measure Patient Functional Ability After Outpatient Surgery

- Satisfaction depends on level of adverse experience*, but not on preoperative concerns or discordance between concern and experience

*pain, vomiting, nausea, grogginess


Use of Algorithms…

- Enhance clinical performance for drug dosing, preventative care, & other aspects of medical care (Hunt et al., 1998)
- Reduce number of requested tests, questions asked, & elements of physical exam (Patel et al., 2001)
- Improve patient outcomes & decrease costs (Fanning, 2002; De Jonghe et al., 2005)
PONV: Consensus Guidelines – Revised 2006

Objective:
Development of comprehensive, clinically useful guidelines for PONV management by an international multidisciplinary expert panel of anesthesiologists, a surgeon, a nurse anesthetist, a perioperative nurse, a biostatistician and a pharmacist.


Consensus Guidelines

PONV Consensus Guidelines Revised-2006

• An additional 250 comparative antiemetic trials have been published since last panel.
• Supported by Society for Ambulatory Anesthesia (SAMBA)
• The current medical literature was critically evaluated
Guideline 1.
Identify Patients at risk for PONV:
Patient-specific risk factors

- Female gender (RCT)
- Nonsmoking status (RCT)
- History of PONV/motion sickness (RCT)

Consensus Guidelines – Revised 2006

RCT = randomized controlled trial

Additional Patient-Specific Risk Factors

Additional Predictors of PONV

- Younger age (in adults)
- History of migraine
- Coexisting medical conditions
- Presence of pain

Anesthetic Risk Factors

- Use of volatile anesthetics for 2 hours post anesthesia (RCT)
- Nitrous oxide (SR)
- Use of intraoperative (SR) and postoperative opioids (RCT)

SR = systematic review

Surgical Risk Factors

- Duration of surgery (each 30 minute increase in duration increases PONV risk by 60%, so that a baseline risk of 10% is increased by 16% after 30 minutes)
- Type of surgery


<table>
<thead>
<tr>
<th>Type of Surgical Procedure as Risk Factor</th>
<th>Odds Ratio</th>
<th>CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthopedics (shoulder)</td>
<td>5.91</td>
<td>3.4–10.3</td>
<td>P=0.001</td>
</tr>
<tr>
<td>Ophthalmologic</td>
<td>5.85</td>
<td>3.8–9.0</td>
<td>P=0.001</td>
</tr>
<tr>
<td>ENT</td>
<td>4.39</td>
<td>2.1–9.2</td>
<td>P=0.001</td>
</tr>
<tr>
<td>Gynecologic (non-D&amp;C)</td>
<td>3.31</td>
<td>2.3–4.8</td>
<td>P=0.001</td>
</tr>
<tr>
<td>Orthopedic (knee)</td>
<td>2.82</td>
<td>1.9–4.2</td>
<td>P=0.001</td>
</tr>
</tbody>
</table>

CI=confidence interval
Type of Anesthesia as Risk Factor

General Anesthesia 11x Higher Risk of PONV

- General anesthesia increased risk of PONV by 11 times compared with monitored anesthesia care, local anesthesia, regional anesthesia, or chronic pain block.


Risk Factors and Stratification

Risk factors include: Female gender, history of motion sickness, nonsmoking status, longer (>60 minutes) duration of surgery, laparoscopy, laparotomy, plastic surgery, major breast surgery, craniofacial surgery, otolaryngologic procedures, strabismus surgery.


Simplified Risk Factors for PONV

Major Risk Factors
1. Female gender
2. Postoperative opioid use
3. Non-smoking
4. History of PONV or motion sickness

- 1 point for each factor

Risk of PONV

Guideline 2. Reduce Baseline Risk Factors for PONV

- Use of regional anesthesia (RCT)
- Use of propofol for induction and maintenance of anesthesia (SR)
- Avoidance of nitrous oxide (RCT/SR)
- Avoidance of volatile anesthetics (RCT)
- Minimization of intraoperative (SR) and postoperative opioids (RCT)
- Minimization of neostigmine (SR)

Consensus Guidelines – Revised 2006

Guideline 3. Administer PONV Prophylaxis using one to two interventions in adults with moderate risk for PONV

Consensus Guidelines – Revised 2006
Families of Antiemetic Drugs

- Phenothiazines (Dopamine D2 receptor)
  - Chlorpromazine
  - Prochlorperazine
  - Promethazine
- Butyrophenones (Dopamine D2 receptor)
  - Droperidol
  - Haloperidol
- Benzamides (Dopamine D2 receptor)
  - Metoclopramide
- Antihistamines (Histamine)
  - Dimenhydrinate
  - Hydroxyzine
  - Diphenhydramine
- 5-HT3 antagonists (Serotonin)
  - Dolasetron
  - Granisetron
  - Ondansetron
  - Palonosetron
- Steroids (Receptor is unclear)
  - Dexamethasone
- NK1-receptor antagonists
  - Aprepitant

Antiemetic Doses and Timing for Administration in Adults

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose</th>
<th>Evidence</th>
<th>Timing</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transdermal</td>
<td>1 mg IV</td>
<td>RCT (Bailey, 1990)</td>
<td>Prior evening or 4 hrs before surgery</td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>10.5 mg IV</td>
<td>RCT (Buttner, 2004)</td>
<td>Expert opinion</td>
<td></td>
</tr>
<tr>
<td>Transdermal</td>
<td>0.025-0.05 mg IV</td>
<td>RCT (Wilson, 1996; Mikawa, 1997; D'Angelo, 2005)</td>
<td>End of surgery</td>
<td></td>
</tr>
<tr>
<td>Tropisetron</td>
<td>5 mg IV</td>
<td>RCT (Tramer, 1997)</td>
<td>Evidence, evidence, evidence</td>
<td></td>
</tr>
<tr>
<td>Transdermal</td>
<td>6-8 mg IV</td>
<td>RCT (Wilson, 1996)</td>
<td>End of surgery</td>
<td></td>
</tr>
<tr>
<td>Droperidol*</td>
<td>4-5 mg IV</td>
<td>RCT (Bailey, 1990)</td>
<td>End of surgery</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.5-2 mg IM/IV</td>
<td>SR (Kranke, 2002)</td>
<td>Evidence, evidence, evidence</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.5-2 mg IM/IV</td>
<td>SR (Kranke, 2002)</td>
<td>Evidence, evidence, evidence</td>
<td></td>
</tr>
<tr>
<td>Scopolamine</td>
<td>Transdermal patch</td>
<td>Evidence</td>
<td>Timing may not affect efficacy</td>
<td></td>
</tr>
<tr>
<td>Tropisetron</td>
<td>12.5 mg IV</td>
<td>RCT (Wilson, 1996)</td>
<td>End of surgery</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>5 mg IV</td>
<td>RCT (DiBruijn, 1992)</td>
<td>End of surgery</td>
<td></td>
</tr>
<tr>
<td>Granisetron</td>
<td>0.3-0.6 mg IV</td>
<td>RCT (Wilson, 1996)</td>
<td>End of surgery</td>
<td></td>
</tr>
<tr>
<td>Dolasetron</td>
<td>4 mg IV</td>
<td>RCT (Graczyk, 1997)</td>
<td>End of surgery</td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td>0.1-0.3 mg/kg IV</td>
<td>RCT (Tramer, 1997)</td>
<td>End of surgery</td>
<td></td>
</tr>
</tbody>
</table>

Future Therapies

- While there are numerous agents currently being used for PONV the incidence still remains unacceptably high.
- It is hoped that as newer agents are developed the incidence of PONV will be decreased.
- New agents
  - Second generation 5HT3 antagonists -(not approved for PONV)
  - NK1 receptor antagonists –Aprepitant-(approved for PONV)
  - Cannabinoids
  - Peripheral opioid antagonist
  - Opioid antagonists

Lack of Evidence

- Metoclopramide 10mg
- Ginger root
- Hypnosis

Guideline 4. Administer prophylactic therapy with combination/multimodal therapy in patients at high risk for PONV

5-HT₃ + Droperidol =

5-HT₃ + Dexamethasone =

Droperidol + Dexamethasone

Guideline 5. Administer prophylactic antiemetic therapy to children at increased risk for PONV

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron*</td>
<td>50 – 100 mg kg⁻¹ up to 4 mg</td>
<td>SR (Tramer. 1997:17:317–80; Tramer, 2000)</td>
</tr>
<tr>
<td>Dolasetron</td>
<td>350 mg kg⁻¹ up to 12.5 mg</td>
<td>RCT (Huang, 2003; Tramer, 2003)</td>
</tr>
<tr>
<td>Granisetron</td>
<td>40 mg kg⁻¹ up to 0.6 mg</td>
<td>RCT (Cowan, 2004)</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>150 mg kg⁻¹ up to 5 mg</td>
<td>SR (Verde, 1993;10:158–62; Kranke, 2003; Mathew, 2006)</td>
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<tr>
<td>Droperidol**</td>
<td>50 - 75 mg kg⁻¹ up to 1.25 mg</td>
<td>SR (Verde, 1995:17:527-81)</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>0.5 mg/kg⁻¹</td>
<td>SR (Hua, 1992:16:230-44)</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>70 mg kg⁻¹ up to 5 mg</td>
<td>SR (Verde, 1996)</td>
</tr>
</tbody>
</table>
Use of Combination Therapy in Children is Most Effective

- Ondansetron, 0.05 mg/kg, + dex, 0.15 mg/kg
- Ondansetron, 0.1 mg/kg, + droperidol, 0.15 mg/kg
- Tropisetron, 0.1 mg/kg, + dex, 0.5 mg/kg
- Granisetron, 0.04 mg/kg, + droperidol, 0.05 mg/kg
- Granisetron, 0.04 mg/kg, + dex, 0.15 mg/kg

Guideline 6. Provide antiemetic treatment to patients with PONV who did not receive prophylaxis or in whom prophylaxis failed

- If prophylaxis fails or was not received; use antiemetic from a different class than prophylactic agent.
- Readminister only if greater than 6 hrs after PACU; do not readminister dexamethasone or scopolamine.
Ondansetron vs. Placebo for Treatment

Prophylactic Treatment


Pathophysiology of PONV


ASPN’S Evidence-Based Clinical Practice Guideline for the Prevention and Management of PONV/PDNV

- Evidence for risk factors, prophylactic and treatment therapies
- Evidence for traditional therapeutic management, complementary modalities
- Identify areas of needed research


Economics of PONV

The Hospital Perspective: PONV Prophylaxis is Cost Effective

Median cost per patient*
- Ondansetron 4 mg: $16.44
- Droperidol 0.625 mg: $0.63
- Droperidol 1.25 mg: $0.51
- Placebo: $51.20

* Includes cost for drug acquisition, materials, personnel time, PACU delay, and hospital admission.

P = 0.001, active treatment groups vs placebo

New and Emerging Therapies for Preventing Postoperative Nausea and Vomiting

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Dr. Golembiewski obtained her Bachelor of Science in Pharmacy and Doctor of Pharmacy degrees from the University of Illinois at Chicago College of Pharmacy. At UIC, she participates in the education of the anesthesiology resident physicians, pharmacy students, and pharmacy residents. She also conducts research in postoperative pain management, postoperative nausea and vomiting, sickle cell pain management, and intraoperative anesthetic medications at the UIC. Her additional responsibilities include committee work, medication guideline development, cost-containment, and quality improvement initiatives in the perioperative setting.

Dr. Golembiewski has published on perioperative pharmacy topics in peer-reviewed journals and has written several book chapters in pharmacy and medical textbooks, such as *Lexi-Comp’s Anesthesia and Critical Care Handbook*, *Applied Therapeutics – The Clinical Use of Drugs*, and *ASHP’s PharmPrep – Case Based Board Review*. She serves on the editorial boards of *Anesthesia Today* and *Pharmacy Practice News*. She is also a reviewer for several pharmacy, medicine, and nursing journals and textbooks.
Current and Emerging Therapeutic Options for Prevention of PONV: Developing Strategies for Optimal Outcomes

Julie Golembiewski, Pharm.D.
Clinical Associate Professor
Departments of Pharmacy Practice and Anesthesiology
University of Illinois at Chicago

Antiemetic Agents
“The Oldies”

- Droperidol
- Serotonin Antagonists
  – Ondansetron, dolasetron, granisetron
- Dexamethasone
- Transdermal scopolamine
- Metoclopramide

Droperidol: Results of Meta-Analyses

- Anti-nausea effect
  – Droperidol is consistently better than ondansetron
    - Dose-dependent effect
      – Need at least 0.5 mg
      – Improved vomiting efficacy with doses of ≥ 0.75 mg
- Anti-vomiting effect
  – Ondansetron is consistently better than droperidol

Anesthesiology 1997;87:1277.
Droperidol's Black-Box Warning

- Due to its potential for serious proarrhythmic effects and death:
  - Reserve for treatment who failed other treatments.
  - 12-lead ECG prior to administration.
  - Continue ECG monitoring for 2-3 hours after administering droperidol.

QTc Prolongation: Droperidol vs. Ondansetron

- In PACU, patient received either 0.75 mg droperidol or 4 mg ondansetron for PONV
- Results:
  - Both drugs significantly prolonged QTc interval
    - Droperidol: 17 ± 9 ms (occurred after 2 min.)
    - Ondansetron: 20 ± 13 ms (occurred after 3 min.)
  - QTc interval was significantly lower after 90 minutes in both groups
- Authors concluded:
  - Both drugs prolonged QTc interval to the same extent
  - Safety of serotonin antagonists may not be superior to low dose droperidol


Haloperidol vs. Ondansetron

- 244 inpatients and outpatients previously planned to receive PONV prophylaxis
- 1 mg haloperidol vs. 4 mg ondansetron, with pre- and post-op 12-lead ECG for measurement of QTc
- Results:
  - No difference in efficacy (70 – 80%)
  - No difference in sedation or QTc prolongation
    - Pre-op % with QTc >450 msec: 7.4% (H) and 8.1% (O)
    - Post-op % with QTc >450 msec: 40.4% (H) and 34.3% (O)
  - No patient had extrapyramidal signs

Anesthesiology 2005;103:A624.
Serotonin Antagonists

• Different components of CYP enzyme system predominate in metabolism of each of these agents

<table>
<thead>
<tr>
<th>Ondansetron</th>
<th>Hydrodolasetron</th>
<th>Granisetron</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4</td>
<td>CYP2D6</td>
<td>CYP3A</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>CYP3A4</td>
<td></td>
</tr>
<tr>
<td>CYP1A1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP1A2</td>
<td></td>
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</tr>
</tbody>
</table>


Impact of CYP2D6 Genotype: Ondansetron

• 250 females received ondansetron for PONV prevention → 88 had nausea, 37 had vomiting
• Incidence of vomiting in:
  – Poor metabolizers: 1/12 (8%)
  – Intermediate metabolizers: 5/30 (17%)
  – Extensive metabolizers: 26/176 (15%)
  – Ultrarapid metabolizers: 5/11 (45%)
• No difference in incidence of nausea
• Conclusion: ultrarapid metabolizers (3 copies) have ↑ incidence of vomiting but not nausea

Anesthesiology 2005;102:543.

Impact of CYP2D6 Genotype: Granisetron vs. Dolasetron

• 150 adults at moderate to high risk for PONV received either 12.5 mg dolasetron or 1 mg granisetron for PONV prevention (all pts received dexamethasone)
• Results:
  – Complete response in PACU
    • No difference between groups (70% response rate)
  – Complete response at 24 hrs
    • 64.7% granisetron group vs. 38.7% dolasetron group (P<0.05); no difference in QOL or patient satisfaction
  – Carriers of duplicated CYP2D6 allele
    • In ultrarapid metabolizers, there were fewer vomiting episodes in patients who received granisetron (P=0.033)

Dexamethasone

• Efficacy
  – NNT to prevent early and late vomiting in adults and children: 7.1
  – NNT to prevent late nausea: 4.3
• No reports of adverse effects


Dexamethasone – Additional Benefits

• 80 patients undergoing laparoscopic cholecystectomy
• 8mg IV dexamethasone vs. placebo pre-op
• Primary endpoints: fatigue and pain
• Results: Dexamethasone significantly reduced:
  – Post-op levels of C-reactive protein
  – Fatigue
  – Pain (during first 24 hours and first post-op week)
  – Nausea and vomiting on day of surgery
  – Duration of convalescence


Effect of Dexamethasone on Blood Glucose – Neurosurgery Patients

• 34 non-diabetic patient undergoing craniotomy (3 groups)
  – On dexamethasone pre-op; continued intra-op
  – Intra-op dex only (10 mg IV on induction; 4mg IV 6 hrs later)
  – No dexamethasone at all
• BG concentration changes documented for 12 hours

Pts who received only intra- and post-op dexamethasone had the largest peak BG concentrations.

**Effect of Antiemetic Dose of Dexamethasone on Blood Glucose**

- Non-diabetic patients undergoing inpatient surgery received 8 mg IV dexamethasone (N=20) or 4 mg IV ondansetron (N=22).
- Blood glucose measured at baseline, 2 hr, 4hr, and 24 hrs.

<table>
<thead>
<tr>
<th>Time</th>
<th>Dexamethasone group (N=20)</th>
<th>Ondansetron group (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>95 ± 4 mg/dl</td>
<td>93 ± 3 mg/dl</td>
</tr>
<tr>
<td>2 hours</td>
<td>8 ± 8 mg/dl</td>
<td>24 ± 6 mg/dl</td>
</tr>
<tr>
<td>4 hours</td>
<td>44 ± 12 mg/dl</td>
<td>40 ± 7 mg/dl</td>
</tr>
<tr>
<td>24 hours</td>
<td>18 ± 13 mg/dl</td>
<td>18 ± 8 mg/dl</td>
</tr>
</tbody>
</table>

* Change from baseline

*Anesthesiology 2006;105:A569.*

*Anesthesiology 2005;100:1129.*
Effect of Antiemetic Dose of Dexamethasone on Blood Glucose (cont.)

- 63 pts undergoing abdominal surgery
  - 32 non-diabetics and 31 type-2 diabetics (not receiving insulin) received 10 mg IV dexamethasone at induction
  - Blood glucose measured at induction and every hour for 4 hours
- Results:

  Br J Anaesth 2006;97:164.

Transdermal Scopolamine (TDS) vs. Ondansetron

- 78 obese females undergoing laparoscopic gastric bypass
- Blinded, TDS vs. ondansetron 4mg
- 48-hour study period
- Results:
  - No difference in recovery time, incidence of PONV, nausea score, rescue antiemetic requirements, and side effects
- Authors concluded: Ondansetron and TDS are equally effective, but TDS is more cost-effective for routine prophylaxis

IARS 2005, S-163.
Ondansetron +/- Transdermal Scopolamine

- High risk patients undergoing ambulatory cosmetic surgery
  - All patients received 4 mg IV ondansetron
  - Randomized to receive TDS or placebo patch
- 24-hr study period
- Results:
  - First 3 hrs: No difference between groups
  - After discharge (4 – 24 hrs): Significantly less nausea in patients who received scopolamine (P<0.05)
  - Admission to hospital for uncontrolled nausea:
    - 1 patient from scopolamine group
    - 3 patients from ondansetron group

Anesthesiology 2006;105:A1592.

Metoclopramide

- Meta-analysis ¹
  - Less effective than ondansetron or droperidol
  - Most studies administered it at induction
- Systematic review ²
  - More effective than placebo (all doses)
    - RR for PONV: 0.76
  - Depending on P value and control risk, the effect of 10 mg IV metoclopramide may not be enough to be detected

¹ Anesth Analg 1999;88:1370.

Metoclopramide (con’t)

- 3140 patients randomized to receive 8 mg dexamethasone alone or with 10 mg, 25 mg, or 50 mg metoclopramide
- 24-hr study period

BMJ 2006;333:324.
Factorial Trial of Six Interventions for Preventing PONV

- 5,199 adults randomized (28 centers)
  - Elective surgery with general anesthesia (≥ 1 hour)
  - High risk for PONV defined as the presence of at least two of the following risk factors:
    - Female sex
    - Nonsmoker
    - Previous history of PONV or motion sickness
    - Anticipated use of postoperative opioids

The Study Protocol

- Simultaneously evaluated 6 prophylactic interventions and their combinations:
  - Ondansetron 4mg IV vs. no ondansetron
  - Dexamethasone 4mg IV vs. no dexamethasone
  - Droperidol 1.25mg IV vs. no droperidol
  - Propofol vs. volatile anesthetic
  - Nitrogen vs. nitrous oxide
  - Remifentanil vs. fentanyl
- Primary outcome: nausea and vomiting within 24 hours after surgery

Results

- Ondansetron, dexamethasone, and droperidol had comparable efficacy
  - Each reduced PONV risk by about 26%
- Propofol reduced PONV risk by 19%
- Nitrogen reduced PONV risk by 12%
- Remifentanil did not reduce risk compared to fentanyl
Results (continued)

<table>
<thead>
<tr>
<th>Number of Antiemetics</th>
<th>Incidence of PONV</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>52%</td>
</tr>
<tr>
<td>One</td>
<td>37%</td>
</tr>
<tr>
<td>Two</td>
<td>28%</td>
</tr>
<tr>
<td>Three</td>
<td>22%</td>
</tr>
</tbody>
</table>

There were no significant differences between the antiemetics or pairs of antiemetics.


Aprepitant
“The new”

Aprepitant vs. Ondansetron
(30 centers, Phase III trial)

- 805 pts undergoing open abdominal surgery
- Randomized to receive 125 mg oral aprepitant, 40 mg oral aprepitant, or 4 mg IV ondansetron
- Primary endpoint: complete response (0-24 hrs)
- 48-hr study period
- Results
  - No difference in primary endpoint between 3 groups
  - Aprepitant (both doses) provided better protection against vomiting in:
    - First 24 hrs (95% and 90% vs. 74%, P<0.001)
    - 48 hrs (93% and 85% vs. 67%, P<0.001)
  - No difference between groups in:
    - Use of rescue therapy (0-24 hrs)
    - Tolerability

Anesthesiology 2005;103:A769.
Aprepitant vs. Ondansetron: 
Post Hoc Analyses from Two Trials

• 1,599 pts undergoing open abdominal surgery
• Randomized to receive 125 mg oral aprepitant, 40 mg oral aprepitant, or 4 mg IV ondansetron
• Compared to ondansetron, 40 mg oral aprepitant:
  – ↓ significant nausea (P=0.009)
  – ↓ nausea (P=0.035)
  – ↓ vomiting (P<0.001)
  – ↓ nausea and vomiting (P=0.023)
  – ↓ nausea, vomiting, and use of rescue therapy (P=0.027)

Questions and Discussion

• We welcome your questions.
• Staff will collect written question cards.
• Please approach a standing microphone in the aisle.
• Please complete the program evaluation located in your handout and leave with staff as you exit.
• Thank you for your attention.
• Join us again for CE in the Mornings.
New and Emerging Therapies for Preventing Postoperative Nausea and Vomiting

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