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PONV, PDNV and Long QT Syndrome: Balancing Risk and Benefit

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Stem Case and Key Questions Content

A 36 year-old woman is scheduled for elective tubal ligation at an ambulatory outpatient surgicenter. She has a history significant for postoperative nausea and vomiting requiring unanticipated hospitalization.

Past Surgical History: PONV with laparoscopic cholecystectomy

1) What are the patient and surgical risk factors for patients who develop PONV? Is this different for children? What is the strongest predictor? Does surgery type matter?

2) How might you tailor prophylaxis and rescue antiemetic use based on a patient's risk?

Her past medical history is also significant for hereditary long-QT syndrome, for which she is asymptomatic.

Past Medical History: Long-QT syndrome, non-smoker

Physical Examination: HR 65 bpm, BP 110/60, QTc 470 ms, Ht 5'6", Wt 135 lbs

Labs: Na 140 meq/L, K 3.2 meq/L, Ca 9.8 mg/dL

3) What is long-QT syndrome and is it clinically significant? What anesthetic agents and antiemetics are known to prolong the QT interval?

4) What is Torsades de Pointes and how can it be prevented or treated?

The patient informs you that she failed multiple antiemetics during her last surgery and she asks you what strategies you will employ to prevent nausea and vomiting so that she can go home after surgery.

5) What anesthetic techniques and antiemetic agents are available? How do they work and how do you choose which ones to use? Are the effects additive or synergistic?

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The patient mentions to you that she lives in a rural area and she is concerned about postdischarge nausea and vomiting as she will be hours away from the nearest hospital and may not be able to tolerate oral rescue agents. She would like to know how you plan to address this possibility.

6) What is the incidence of PDNV? How does PDNV differ from PONV? Are the risk factors different than PONV?

7) What antiemetics are most likely to specifically address PDNV?

8) What additional strategies exist to prevent PONV and PDNV in the high risk patient? What is the supporting evidence?

Model Discussion Content

- Postoperative nausea and vomiting (PONV) has a 20-30% occurrence overall and is rated by many patients as more concerning than postoperative pain (1). It is a leading cause of prolonged post-anesthesia care unit (PACU) admission and unanticipated hospitalization. Risk factors for developing PONV include female gender, non-smoking, history of PONV/motion sickness, and PACU opioid use. Using the Apfel score, 0-4 of these risk factors yields a 10, 20, 40, 60, or 80% risk (2). Also likely to predict PONV are duration of exposure to general anesthetic and younger age. In children, a similar risk score exists with the validated factors being strabismus surgery, age > 3 years, surgery > 30 minutes, and history of PONV in the child or immediate relatives (3). Accordingly, prophylaxis can rationally be tailored based on risk with one intervention planned for each risk factor present, a sentiment echoed in the Society of Ambulatory Surgery 2007 PONV consensus guidelines (3). Of note, each antiemetic intervention decreases incidence of PONV by 20-30% and this effect is additive, not synergistic (4). Thus each additional intervention yields less benefit while introducing side effects associated with the medication, hence avoiding the “kitchen sink” approach to PONV prophylaxis. Also, when rescue is instituted it is most effective if it is from a different class than recently trialed interventions, which speaks to the need for understanding of antiemetic mechanisms of action.

- More recently, with increases in ambulatory surgeries there has been a focus on postdischarge nausea and vomiting (PDNV). This occurrence can be of particular concern as patients lack intravenous access and may not tolerate oral rescue medications, leading to unnecessary suffering or emergency department visits. A recent multicenter study demonstrated a striking incidence of PDNV of 35% over the first 3 days after discharge from the hospital for ambulatory surgery. Risk factors were similar to PONV but non-smoking status was not a significant predictor in this analysis. Female gender, age > 50 yrs, history of PONV, PACU opioid use, and PACU PONV accounted for 10%, 20%, 30%, 50%, 60%, and 80% risk when 0-5 risk factors were present (1). Again, duration of general anesthesia, higher dose of perioperative opioids, and laparoscopic approach (but not specific surgical type) were also risk factors.

- Nausea and vomiting is believed to be centrally mediated in three distinct areas. The

chemoreceptor trigger zone in the area postrema is unique in that it resides outside the blood-brain barrier and allows for detection of noxious stimuli in the blood. This is the likely site of 5HT₃-receptor antagonist activity. The nucleus tractus solitarius in the brainstem detects input from vagal and vestibular afferents and is the site of NK₁-receptor antagonist activity. And the central pattern generator in the lateral reticular formation of the medulla appears to be the site of centrally acting agents (1, 5).

- The most commonly used antiemetics are the serotonin antagonists, the most well-described being ondansetron. Ondansetron is delivered as a 4 mg dose IV or po, is non-sedative, and has a $\frac{1}{2}$ life of 4 hours. Re-dosing for rescue is ineffective if within 4 hours and there is some evidence for rebound PDNV in patients administered ondansetron for rescue in the PACU. Ondansetron also prolongs the QT interval. Despite these drawbacks, it is generally well-tolerated. Other antiemetics in this class include dolasetron, granisetron, tropisetron, and ramosetron.

- Butyrophenones such as droperidol were commonly used at doses of 0.625-2.5 mg IV. They are centrally acting D₂-receptor antagonists and are markedly sedating. Use has dwindled due to a United States Food and Drug Administration (FDA) black box warning regarding risk of QT prolongation and Torsades de Pointes, necessitating 2-3 hours of ECG monitoring after dosing. Of note, this warning was based on data associated with large doses (25-250 mg) and during the period of surveillance there was only 1 death out of 273 adverse events with low dose droperidol and documented long QT and arrhythmia over 4 years with 11-25 million doses per year administered (6). As a result of the black box warning, many practitioners began substituting haloperidol 0.5-2 mg IV with similar efficacy, however similar QT prolongation is reported with this medication (again, at higher dosing as with droperidol) and subsequently a FDA warning, though not a black box, was issued (3).

- Dopamine antagonists such as metoclopramide are often used but generally at doses insufficient to prevent PONV. 25-50 mg IV or po, not 10 mg, has been shown to reduce PONV similarly to other agents, however, extrapyramidal symptoms, particularly in the elderly, can be limiting.

- Anesthetic techniques such as Total Intravenous Anesthesia significantly decrease PONV. This effect is most clear in the first 2 hrs postoperatively but may not be beneficial thereafter. Total intravenous anesthesia (TIVA) does not increase QT, which differs from inhalational agents. Nitrous oxide is often thought to be exceedingly emetogenic however this effect seems to be no more pronounced than inhaled agents when examined critically. Regional anesthesia can decrease inhalation agent use and postoperative opioids, which also effectively decreases PONV. Finally, acupoint P6 stimulation may hold promise for prevention of PONV with a number needed to treat (NNT) of 11 for patients at 30% risk, and 5 for patients at 70% risk based on a recent Cochrane Review. This can easily be accomplished by most anesthesiologists simply by placing the commonly used nerve stimulator over the radial rather than ulnar side of the wrist (7).

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- Certain antiemetic agents may hold particular benefit for PDNV given prolonged duration of action, ability to be given prophylactically, and non-oral delivery systems. Palonosetron is a 5HT₃-receptor antagonist with a $\frac{1}{2}$ life of 40 hours and a single dose of 0.075 mg has been shown to decrease PDNV over 72 hours. It is also the only medication from this class that does not prolong the QT interval. The cholinergic antagonist scopolamine is available as a 1.5 mg patch q 72 hours. The transdermal delivery system decreased PONV over 24 hours in one study and can be applied prior to surgery. Side effects include dry mouth, tachycardia, blurry vision, and confusion generally most apparent at 48-72 hours. The glucocorticoid dexamethasone is often used at a dose of 4-8 mg IV. The largest effect on nausea appears to be on late PONV and PDNV, not early PONV, and it is ineffective as a rescue medication. Finally, neurokinin-1 receptor antagonists such as aprepitant 40 mg po or fosaprepitant IV are now available. They result in a striking 90% decrease in emesis and are non-sedative with no QT prolongation. The $\frac{1}{2}$ life is 9-13 hrs. Cost can be prohibitive, however.

- Many alternative treatment modalities have been tried to prevent nausea and vomiting while minimizing cost. These have included non-pharmacologic options as well as re-trialing older medications from different classes (e.g., analgesics, anxiolytics). The following have unfortunately demonstrated limited effect to date: gastric decompression, supplemental oxygen, ginger, nicotine patch, proton pump inhibitors, and low-dose neostigmine reversal. However, midazolam 2 mg IV given at the end of surgery, gabapentin 600-800 mg po 1-2 hours pre-operatively, and dimenhydrinate 1 mg/kg IV have demonstrated similar efficacy against PONV as more commonly used interventions and at decreased cost and with well-defined safety profiles (3).

- Many antiemetics are associated with prolongation of the QT interval. This is of particular concern for patients with long-QT syndrome, which can be hereditary or acquired. Long-QT syndrome is defined as a QT > 440 ms for men and QT > 460 ms for women. It is corrected for heart rate, averaged over 6-10 beats, and measured from the beginning of the Q wave to the end of the T wave, mostly reflecting repolarization. There is a two-fold increase in syncope or sudden cardiac death associated with a QTc > 460 ms and a ten-fold increase with QTc > 500 ms. 70% of these events occur in women, later in life (8). Medications known to prolong the QT interval should be avoided, including quinidine, methadone (dose-related effect), flouroquinolones, antifungals, and volatile anesthetics.

- Torsades de Pointes is the most feared complication of long QT syndrome, resulting from early after depolarizations and R on T phenomenon leading to polymorphic ventricular tachycardia with "twisting of points." It is more common in conjunction with bradycardia, PVCs, and compensatory pauses. Risk can be decreased by decreasing sympathetic tone (such as via stellate ganglion block, sympathectomy, or beta-blockers). Pacers or AICDs may be employed. Hypokalemia, hypomagnesemia, and hypocalcemia should be corrected prior to surgery to minimize QT prolongation. Treatment includes defibrillation if unstable. Consider vasopressin in place of epinephrine for resuscitation to minimize cardiac excitation, magnesium 2 g over 2-5 minutes and infusion 2-4 mg/min, and atrial pacing (narrow QRS, shorter QT) if needed (8).

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