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Treating Breakthrough PONV: A Review of Therapeutic Approaches, Considerations, and Guidelines

Chapter 1: Treating Breakthrough PONV: A Review of Therapeutic Approaches, Considerations, and Guidelines

Dr. Gan:
Hello, I'm TJ Gan and I am Head of the Division of Anesthesiology and Perioperative Medicine, Critical Care and Pain Medicine at the University of Texas MD Anderson Cancer Center in Houston.

We take care of patients with all types of cancer and perform over thirty thousand surgical procedures each year.

Unfortunately, many patients develop postoperative nausea and vomiting, or PONV, despite our best efforts to reduce the incidence.[1,2]

Patients have told us that PONV is what they want to avoid most after surgery, surpassing even their concern of pain, and is the most common reason for their dissatisfaction.[3,4]

In enhanced recovery after surgery or ERAS, we focus on using evidence-based techniques to provide the best care for our surgical patients to ensure the speediest recovery with the least complications.

With respect to PONV management, we routinely provide multimodal, antiemetic therapy based on patient's risk factors for developing PONV to minimize the incidence.[1] If patients develop breakthrough PONV, we promptly and aggressively treat it with a different class from what we have given for prevention.[1]

Prompt treatment of PONV not only relieves patients of distressing PONV symptoms, but it also reduces the length of stay in the PACU and saves healthcare costs.[2,5]

ERAS protocols in various types of procedures have been shown to improve the quality of care, reduce complications, and speed up the recovery process so patients can get on with their normal activities.[1]

Every successful ERAS protocol needs to incorporate a PONV management protocol, both for prevention and treatment of breakthrough PONV.[1] The PONV management strategies implemented in the published enhanced recovery protocols, or ERPs, are consistent with the principles in our consensus guidelines, which include risk reduction, prophylaxis, and treatment.[1]

Medications used should target different receptor sites to achieve multimodal benefit, and the treatment of established PONV should be prompt and aggressive.[1]

Recently, the Anesthesia Patient Safety Foundation released an article regarding the dopamine-2 antagonist antiemetics for PONV.[6]

They have established that there are at least three distinct structural subclasses of dopamine-2 antagonists. They include substituted benzamides, butyrophenones, and phenothiazines.[6-8]

One key pharmacologic property that differs between the subclasses is central nervous system penetrability. Sedation, neuropsychiatric effects, extrapyramidal symptoms, and neuroleptic malignant syndrome may result due to CNS penetration by D_2 antagonist antiemetics.[6] Another key pharmacokinetic property is the binding affinity for potassium ion channels. A high binding affinity of D_2 antagonists to potassium ion channels is more likely to cause QT prolongation and torsade de pointes.[6] Therefore, pharmacokinetic properties of D_2 antagonists should be considered when selecting an antiemetic for your patients.

Barhemsys is the trade name for amisulpride. It is an FDA-approved antiemetic for the prevention and treatment of PONV in patients who have or have not received prophylaxis.[9]

Amisulpride is a selective dopamine-2 and dopamine-3 receptor antagonist benzamide with no appreciable affinity for any other receptors at doses used for PONV.[9,10] It exhibits regional preference for D_2 and D_3 receptors in limbic but not striatal structures, which are involved in control of movement and have been implicated in the occurrence of extrapyramidal symptoms.[10-12]

Barhemsys has an elimination half-life of 4 to 5 hours, plasma protein binding of 25 percent to 30 percent, and it is not metabolized by major cytochrome P450 enzymes.[9] These characteristics indicate a decreased potential for interaction with other protein-bound agents and agents metabolized by the cytochrome P450 system.[9]

Barhemsys has been shown to be effective in both prevention and treatment of PONV in four large clinical trials involving inpatients and outpatients who are at high risk for developing PONV.[9]

The most recent PONV consensus guidelines recommend using an antiemetic that has not been used for prevention to treat patients who have failed prophylaxis.[1] Since antiemetics such as ondansetron and dexamethasone are routinely used for the prevention of PONV, Barhemsys is suited for treating breakthrough PONV since it is a different pharmacological class.[1,2,9]

Recently my colleagues and I published an article in Medscape where we summarized the current evidence on PONV rescue treatment from a systematic review.[13] For many antiemetics currently used in PONV rescue, significant uncertainty remains around effective dose range, speed of onset, and duration of effect.[13] So, for patients needing rescue treatment, options are limited due to a lack of strong clinical evidence that establishes clinical efficacy.

Additionally, the commonly used prophylactic antiemetics may have unwanted side effects, such as sedation, which could result in delayed patient throughput when used as a rescue treatment.[13] However, the efficacy and safety of Barhemsys 10 milligrams, when used in this setting, are supported by a large clinical trial that enrolled more than seven hundred patients who failed prophylaxis.[2,9]

The results showed that forty-two percent of Barhemsys 10 milligram-treated patients met the criteria for complete response at twenty-four hours compared with twenty-nine percent of placebo-treated patients, while seventy percent of Barhemsys 10 milligram-treated patients met the criteria for complete response at 2 hours after receiving treatment compared with forty-nine percent of placebo-treated patients.[2,9]

Additionally, Barhemsys 10 milligram-treated patients had thirty-five minutes shorter mean PACU length of stay and six hours shorter mean hospital length of stay than placebo-treated patients.[2]

Regarding the safety profile, the most common adverse reaction reported for Barhemsys 10 milligrams and at a higher rate than placebo was infusion site pain, with six percent compared to four percent, respectively.[9] Treatment-related sedation or sedation-like reactions were not reported in patients who received Barhemsys in the clinical trials.[14]

The full Important Safety Information, including contraindication and QT prolongation warning, will be covered in Chapter 3.

In summary, the study results demonstrated that a single 10 milligram dose of intravenous Barhemsys is safe and effective as a rescue treatment for PONV in patients who have failed prior prophylaxis.[2,9] Therefore, we sought P&T approval for Barhemsys to be used in breakthrough PONV.

Thank you for taking the time to watch this video. To learn more about Barhemsys, I encourage you to watch the additional chapters where healthcare providers share their clinical experience with Barhemsys.

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Chapter 2: Clinical Considerations for a Selective Dopamine D_2/D_3 Receptor Antagonist Antiemetic for Breakthrough PONV

Dr. Riddle:
Hello, I'm Dru Riddle, a certified registered nurse anesthetist, or CRNA, and my primary responsibility in my clinical setting is direct patient care. I work in a community hospital setting, where we perform both outpatient and inpatient procedures, primarily for adults. In our hospital, we have a significant focus on head and neck cancer surgeries.

Additionally, we handle procedures such as transplants, orthopedics, neurosurgery, and cardiovascular surgeries. We also have a large women's hospital, where we provide comprehensive care for women during childbirth, delivery, and ongoing gynecological care.

My role encompasses three key aspects. The first is risk stratification. This involves thoroughly assessing the patient's risk factors for postoperative nausea and vomiting, or PONV, and planning for anesthesia. In my practice, we use the revised Apfel scoring system and are very deliberate about how we stratify risk.[1]

Second, once we know the risk, we anesthesia providers are positioned to address those risk factors appropriately. We can't change a patient's history of motion sickness or gender, but we can certainly modify our anesthesia techniques and use antiemetic prophylaxis to mitigate the likelihood of PONV.[1]

The third piece is treating patients who have breakthrough PONV. Despite a best-case scenario, when guidelines are followed and patients receive multimodal prophylactic treatment, the reality is there are patients who still experience breakthrough nausea and vomiting. So, the third aspect of how I improve care is rescuing patients from nausea and vomiting in a way that they get good relief from nausea. When choosing an antiemetic, I also consider the side effect profile, as side effects may slow down the recovery process.[2]

Additionally, one important thing is setting expectations with your patient on the front end, and communicating well with them, and letting them know that they are high risk. Despite everything we can do and all the interventions and techniques we provide, there's still a chance they could experience nausea afterward.[1-3]

In my 20-plus years of providing anesthesia care, there hasn't been another antiemetic that was FDA approved for the rescue treatment of PONV after failed prophylaxis. So, to treat our patients, we had been using antiemetics that lacked strong clinical evidence, such as prospective trials, to establish their efficacy, safety, and overall risk-benefit profile as a rescue treatment.

In some cases, unresolved breakthrough PONV symptoms could delay discharge.[2] Then in other cases, the antiemetic could effectively treat the symptoms of PONV, but the associated side effects may have delayed discharge.[2] For example, the patients would go back to sleep for the next two hours in the recovery room.

So, when Barhemsys became an option, for me in my practice, it was an opportunity to utilize a drug specifically approved for PONV rescue. Everything else we're doing is off-label. None of the other drugs have FDA approval for rescue treatment of PONV following failed prophylaxis.

As a clinician, I feel comfortable using Barhemsys in patients who need to be rescued from breakthrough PONV. This is because

studies have specifically evaluated its efficacy and safety profile.[3,4] In the pivotal study, the most common adverse reaction reported for Barhemsys 10 mg and at a rate greater than placebo was infusion site pain.[3,4]

The full Important Safety Information, including contraindication and QT prolongation warning, will be covered in Chapter three.

Barhemsys is heavily used in my practice by our recovery room nurses. They've expressed appreciation to me for ordering this drug because we know it may be helpful for our patients, is non-sedating,[4,5] and may ensure smooth throughput without delays due to the complications of PONV.[3]

To anesthesia providers like us, both the clinical study evidence and real-world experience should be considered when making clinical decisions. In my practice, sometimes I have a patient with significant breakthrough nausea and vomiting. In those cases, I'll give the patient a dose of Barhemsys, which may reduce the level of nausea and vomiting to the point that the patient will say, "I feel so much better. Can I please go home?" or "Can I please go to the floor? Can I move on in the process?" So, when patients feel a lot better after getting the drug, that is a clinical win to me.

In addition, internally within our system, we previously administered ondansetron, promethazine, dexamethasone, and haloperidol to treat breakthrough PONV.[6]

Since we had Barhemsys, a colleague of mine initiated an internal data collection for quality improvement. After reviewing data gathered through our electronic health records of outpatient surgeries over a 6-month time period, we found that patients who received Barhemsys for breakthrough PONV do well, as observed by a reduction in PACU length of stay.[6]

I gained this insight from the amazing PACU nurses I've had the privilege to work with. They have shared with me the importance of treating nausea aggressively and promptly. Now, I encourage my colleagues to administer Barhemsys at the earliest sign of post-op nausea, rather than waiting.

Thank you for taking the time to watch this video. To learn more about Barhemsys, I encourage you to watch the additional chapters where healthcare providers share their clinical experience with Barhemsys.

References:

1. Gan TJ, Belani KG, Bergese S, et al. Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting. *Anesth Analg*. 2020;131(2):411-448.
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Chapter 3: Important Safety Information

Announcer:
Barhemsys is a selective dopamine-2 (D_2) and dopamine-3 (D_3) receptor antagonist indicated in adults for:

prevention of postoperative nausea and vomiting (PONV), either alone or in combination with an antiemetic of a different class and

treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or have not received prophylaxis.

Barhemsys is contraindicated in patients with known hypersensitivity to amisulpride.

QT prolongation is a dose- and concentration-dependent result of Barhemsys. The recommended dose of 5 or 10 milligrams should be infused over 1 to 2 minutes.

Avoid Barhemsys in patients with congenital long QT syndrome and in patients taking droperidol.

Electrocardiogram monitoring is recommended in patients with pre-existing arrhythmias/cardiac conduction disorders, electrolyte abnormalities (such as low potassium or low magnesium), congestive heart failure, and in patients taking other medicinal products (such as ondansetron) or with other medical conditions known to prolong the QT interval.

Common adverse reactions reported in ≥ to 2% of adult patients who received Barhemsys 5 mg (N=748) and at a higher rate than placebo (N=741) in clinical trials for the prevention of PONV were: chills (4% vs. 3%), hypokalemia (4% vs. 2%), procedural hypotension (3% vs. 2%), and abdominal distention (2% vs.1%).

Serum prolactin concentrations were measured in one prophylaxis study where 5% (9/176) of Barhemsys-treated patients had increased blood prolactin reported as an adverse reaction compared with 1% (1/166) of placebo-treated patients.

The most common adverse reaction, reported in ≥ 2% of adult patients who received Barhemsys 10 mg (N=418) and at a higher rate than placebo (N=416), in clinical trials for the treatment of PONV was infusion site pain (6% vs. 4%).

Available data with amisulpride use in pregnant women are insufficient to establish a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.

Amisulpride is present in human milk. There are no reports of adverse effects on the breastfed child and no information on the effects of amisulpride on milk production.

Barhemsys may result in an increase in serum prolactin levels, which may lead to a reversible increase in maternal milk production. In a clinical trial, serum prolactin concentrations in females (n=112) increased from a mean of 10 ng/mL at baseline to 32 ng/mL after Barhemsys treatment and from 10 ng/mL to 19 ng/mL in males (n=61). No clinical consequences due to elevated prolactin levels were reported.

To minimize exposure to a breastfed infant, lactating women may consider interrupting breastfeeding and pumping and discarding breast milk for 48 hours after receiving a dose of Barhemsys.

The safety and effectiveness in pediatric patients has not been established.

For geriatric use, no overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Barhemsys causes dose- and concentration-dependent QT prolongation. To avoid potential additive effects, avoid use of Barhemsys in patients taking droperidol.

ECG monitoring is recommended in patients taking other drugs known to prolong the QT interval (such as ondansetron).

And reciprocal antagonism of effects occurs between dopamine agonists (such as levodopa) and Barhemsys. Avoid using levodopa with Barhemsys.

Chapter 4: A Real-World Case of an Approved Rescue Treatment Antiemetic

Dr. Riddle:
Hello, I'm Dru Riddle, a certified registered nurse anesthetist, or CRNA, and my primary responsibility in my clinical setting is direct patient care.

In my early experience with Barhemsys, I had a patient who had undergone multiple surgeries. She was a mom of middle-school age children. She had breast cancer and had to undergo bilateral mastectomies, reconstruction, and radiation treatment. She had been suffering from severe nausea and vomiting after each surgery which caused her to either go home late in the evening or be admitted to the hospital overnight.

When she came in, she expected to have to stay overnight again, even though it was supposed to be an outpatient visit. I reviewed her records and told her that I would try everything available to us to prevent postoperative nausea and vomiting.

Unfortunately, despite appropriate prophylaxis, she still woke up with breakthrough nausea, but this time we administered Barhemsys. After the effects of Barhemsys set in, her face lit up with relief, she expressed how much better she felt, and confirmed that her nausea had improved. She was able to go home and attend her son's basketball game even though she thought she would miss it because of her previous experiences with PONV.

This case demonstrated the real-life impact of this drug.

Thank you for taking the time to watch this video. To learn more about Barhemsys, please visit Barhemsys.com.