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OPEN **Oral Perphenazine 8 mg: A Low-Cost, Efficacious Antiemetic Option**

To the Editor

We congratulate and thank the Fourth Consensus Conference addressing Guidelines for the Management of Postoperative Nausea and Vomiting (PONV).¹ We wholeheartedly agree with its “one major change in this iteration of the guideline...that in adults, the panel consensus is now to implement multimodal PONV prophylaxis in patients with 1 or 2 risk factors, in an attempt to reduce risk of inadequate prophylaxis.” However, since patients with 0 risk factors still have a 10% PONV risk, and because at least 3 non-sedating off-patent inexpensive antiemetics are easily available with minimal side effect burden, we endorse 2 integrated approaches that differ from those presented by the current or previous Consensus Guidelines. First, and principally, we endorse that oral perphenazine 8 mg (OP8) is a low-cost and efficacious tool for prevention of PONV. Second,

we will demonstrate the theoretical value of “the perphenazine-dexamethasone-ondansetron (P-D-O) technique” (OP8, dexamethasone 4 mg intravenous [IV], and ondansetron 4 mg IV), applied to every PONV risk category in such a way that the patient may receive a greater number of PONV-prophylactic agents than what the Consensus Guidelines recommend. Specifically, Consensus “wait and see” patients get 3 antiemetics (P-D-O); those for whom 2 agents are recommended receive 3 agents (P-D-O); and those for whom 3 or 4 agents are recommended all get 4 (P-D-O and an neurokinin-1 receptor-antagonist such as aprepitant [40 mg orally, per os]).

Perphenazine, a phenothiazine with antihistamine properties, at 5 mg IV, was included in the Consensus manuscript’s Table 4, but the IV preparation has not been commercially available in the United States since the early 2000s. We have had extensive experience with OP8 in adults as part of a multimodal antiemetic plan, with its cost at the undersigned authors’ institutions ranging from 50 cents to 2 dollars per dose (US currency). For this low cost per patient, we have previously reported² a 27.2% reduction in the need for IV ondansetron rescue in the postanesthesia care unit (PACU) in nearly 9500 patients from 2002 to 2006.

The implications of a routinely applied P-D-O technique, including for “zero risk factor” patients, is illustrated in a scenario analysis given in the Table. In the classic factorial trial by Apfel et al,³ ondansetron 4 mg, dexamethasone 4 mg, and droperidol 1.25 mg each reduced the risk of PONV by approximately 25%. Based on our 2002–2006 aforementioned² ~25% reduction in need-for-rescue when OP8 was used preoperatively, the Table illustrates that the 3-drug low-cost P-D-O reduces the theoretical risk from 20/200 (10%) to 8/200 (4%) in patients that the Consensus-recommended prophylaxis plan would entail rescue-only without prophylaxis. With the sequential 25% risk reduction per each prophylactic drug, OP8 reduces 20/200 to 15/200, dexamethasone reduces 15/200 to 11/200, and ondansetron reduces 11/200 to 8/200. For patients with 20%–40% risk, we assume 2-agent antiemetic prophylaxis in the Consensus-treated group with ondansetron-dexamethasone (4 mg each IV), and the P-D-O technique-treated group having a 25% further risk reduction than the Consensus-treated group. Finally, for the 60%–80% risk groups where the Consensus guideline is for 3 or 4 antiemetics, we assume half of the Consensus-treated group gets ondansetron-dexamethasone-droperidol 1.25 mg IV for “3 antiemetics,” and the other half of the Consensus-treated group gets ondansetron-dexamethasone-droperidol-aprepitant 40 mg po for “4 antiemetics”; meanwhile, we recommend that P-D-O-aprepitant be given for the 60%–80% risk P-D-O-treated groups.

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Conflicts of Interest: K. Subramaniam worked as a consultant for Octapharma in February 2020, and also receives annual royalties for textbooks from Springer. J. P. Williams is on the Board of Directors for the Allegheny County Medical Society, and for the Pennsylvania Medical Society. He is also on the Council for Medical Education for the American Medical Association. He is also on the Board and an investor for a medical marijuana dispensary. Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the International Anesthesia Research Society. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Table. Scenario Analysis of Side-by-Side Estimated Incidences of PONV When the Consensus Guidelines Are Followed Versus the Proposed P-D-O Technique

| Baseline PONV risk | Consensus-recommended intervention ¹ | Consensus-dosed, PONV cases per 200 ¹ | P-D-O technique, PONV cases per 200 ^{2,3} | PONV prevented with P-D-O, cases per 200 ² |
|--|---|--|--|---|
| 10% | Wait and see | 20 | 8 | 12 |
| 20% | 2 antiemetics | 22 | 16 | 6 |
| 40% | 2 antiemetics | 45 | 32 | 13 |
| 60% | 3 or 4 antiemetics | 25 + 19 = 44 | 38* | 6 |
| 80% | 3 or 4 antiemetics | 34 + 25 = 59 | 51* | 8 |
| Difference in incidence (column total) | | 190 per 1000 | 145 per 1000 | 45 cases per 1000 prevented |

P-D-O technique: perphenazine (8 mg orally before surgery) plus dexamethasone (4 mg IV after induction) plus ondansetron (4 mg IV before emergence). When the Consensus-recommended intervention involves a range of options (eg, 3 or 4 antiemetics), the Consensus-dosed PONV cases per 200 represents a weighted average (half receiving 3, the other half receiving 4), *but for the P-D-O technique, a fourth agent (eg, aprepitant) is what we recommend (and assume) for all cases to have a 25% further risk reduction. Further prospective study is needed to confirm this clinical impression. In this illustration, oral perphenazine 8 mg² is assumed to be a viable substitute to IV droperidol 1.25 mg³, with a ~25% risk reduction. Further prospective study is needed to confirm this clinical impression. No other multimodal techniques are assumed to have been given in either treatment arm (eg, regional or total IV anesthesia). Based on this estimate, 45 fewer patients per 1000 would encounter PONV with the P-D-O technique, representing a 24% risk reduction when compared with the Consensus guideline prophylaxis scheme using ondansetron-dexamethasone, with or without droperidol, and with or without aprepitant, based on the risk estimate category given above.

Abbreviations: IV, intravenous; P-D-O, perphenazine-dexamethasone-ondansetron; PONV, postoperative nausea and vomiting

We previously² encouraged prospective, randomized research with OP8, especially in light of nonseparating benefits in the setting of ambulatory anesthesia fast-tracking and phase 1 PACU bypass, but (13 years after that recommendation) do not anticipate the costs of this research to be underwritten by industry sponsors due to its long-standing availability as a generic preparation, and the implications of a generic medication showing equal efficacy to branded medications. We have found OP8 useful as follows: (1) as a non-sedating antiemetic; (2) as a preventative measure similar to the antihistamine promethazine⁴ against ketamine-induced psychotomimetic effects; and (3) as a safe single-dose drug (only 1.3 extrapyramidal events per 10,000 patients receiving 4–8 mg oral dose, with all events easily treated).⁵ We have published a case series/review² and a randomized trial⁶ of emetic outcomes after the use of OP8 and dexamethasone, with⁶ or not necessarily with² ondansetron (ie, before ondansetron became available as a generic medication).

Additionally, we evaluated the efficacy of single-dose OP8 to a single 40 mg dose of aprepitant given preoperatively in colorectal surgery patients at our academic center within an enhanced recovery protocol, which was designed to mitigate opioid utilization, reduce PONV, and optimize patient recovery.⁷ In this retrospective study, no differences were noted in antiemetic requirement on postoperative days 0 and 1 between patients receiving OP8 versus aprepitant. In addition, when patients were matched for preoperative, procedural, and anesthesia characteristics, no differences were noted in late PONV between patients receiving OP8 versus aprepitant. As enhanced recovery protocols become more widespread and continue to be applied to other surgical specialties, effective PONV prevention is imperative for improving patient outcomes. OP8 deserves to be properly evaluated (by clinical study,

and/or in routine clinical practice) as a part of a cost-effective multimodal enhanced recovery strategy.

As a reminder, metoclopramide should be considered contraindicated for perioperative use if perphenazine is used preoperatively, due to drug interaction risk. According to the Consensus Guideline, "Metoclopramide may be useful in institutions where other dopamine antagonists are not available, but otherwise may not be very efficacious."¹

CONCLUSIONS

The search for the best, cost-effective approach to PONV is far from complete. We recommend that anesthesiology/surgery departments and hospital clinicians on Pharmacy & Therapeutics committees consider in earnest the value of routine preoperative, single-dose OP8, as part of the described P-D-O technique, for patients who have (1) no history of extrapyramidal reactions to similar drugs, (2) no concomitant current long-term prescriptions for antidopaminergic psychiatric drugs, including aripiprazole, and (3) no coexisting Parkinson Disease or cerebral palsy. Our threshold age for dose reduction (0–4 mg instead of 8 mg) is 70 years, if there is no plan for concomitant ketamine use.

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In Response

The consensus panel has read the letter by Williams et al¹ with great interest. In the letter, the authors shared their institutional experience with the use of per os perphenazine for postoperative nausea and vomiting (PONV) prophylaxis, and provided interesting insight into how per os perphenazine could be incorporated in multimodal PONV prophylaxis regimens.

We acknowledge that the availability of intravenous (IV) perphenazine formulation is institution and

country dependent; per os perphenazine on the other hand is readily available in most institutions. This certainly makes per os perphenazine a more viable option in several clinical settings. In addition, due to the availability of the generic formulation, per os perphenazine is likely a more cost-effective intervention. As we have discussed in the consensus guideline, with the increasing adoption of value-based remuneration in health care, the cost-effectiveness of interventions should be taken into consideration, especially when the intervention is applied on a large scale.²

However, as the authors have stated in their letter, there are currently very few published data on the use of per os perphenazine. In a commentary published by the authors, they have discussed the use of both IV and per os perphenazine, in addition to other pharmacological and nonpharmacological interventions.³ However, no control group was included. We identified one other retrospective study by Holder-Murray et al,⁴ which reported that perphenazine monotherapy had similar efficacy as aprepitant on early as well as late PONV. To the best of our knowledge, there are no randomized controlled trials that have investigated the efficacy of per os perphenazine. While it could be argued that available evidence on the efficacy of parenteral perphenazine does indirectly support the use of the per os formulation,⁵ the difference in pharmacokinetics, including onset time and bioavailability, needs to be considered, and may require further studies.⁶

The current consensus guideline expanded on the discussion regarding the practicalities of implementing effective PONV management pathways. As discussed, one of the biggest challenges to effective PONV management is maintaining adherence to the proposed algorithm.^{2,7} Administration of per os premedication in high-throughput presurgical units may be difficult due to staff and infrastructure limitations, and the organizational drive needed to

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