Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Antiemetic Agents***
-January 2021-

Background:

At the Winter 2021 meeting, the Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a drug class review of antiemetic agents. As nausea is a common complaint in numerous conditions, this review included multiple antiemetic drug classes including serotonin receptor antagonists (5-HT_3 RAs), neurokinin-1 receptor antagonists (NK-1 RAs), antihistamines (H1 RAs), antipsychotics, dopamine-2 receptor antagonists (D2 RAs), anticholinergics, cannabinoids, and corticosteroids. Following the clinical review and analyses, the NPTC voted to **add ondansetron** to the IHS National Core Formulary.

Discussion:

The vast majority of studies on antiemetics have been performed in the settings of chemotherapy-induced nausea and vomiting (CINV) or post-operative nausea and vomiting (PONV). Currently, there are four 5-HT_3 RAs available for use in the United States: ondansetron, granisetron, dolasetron, and palonosetron—all of which have equivalent efficacy for CINV in head-to-head trials.[1] Palonosetron has a 40-hour half-life and fewer drug interactions but it is more expensive than ondansetron, unavailable in an oral formulation, and not commonly prescribed. The FDA labels for each 5-HT_3 RA carry warnings regarding QTc prolongation and hypersensitivity. Decades ago, the 5-HT_3 RAs demonstrated superiority to older antiemetics for highly emetogenic CINV (Odds Ratio (OR) 0.60, 95% CI: 0.51-0.70) and moderately emetogenic CINV (OR 0.28, 95% CI: 0.17-0.44). Furthermore, a study published in 1997 reported that 5-HT_3 RAs combined with dexamethasone appeared to further reduce acute vomiting vs. 5-HT_3 RAs alone (OR 0.47, CI: 0.39-0.58).[2]

There are four NK-1 RAs currently available in the US; oral aprepitant and its parenteral prodrug, fosaprepitant, netupitant (available only as a combination oral product with palonosetron), and rolapitant (an oral product with a 180-hour half-life and a different set of interactions from the others). NK-1 RAs have been approved for CINV but as additions to regimens which also include both 5-HT_3 RAs and dexamethasone. While the addition of an NK-1 RA improves the efficacy of regimens with 5-HT_3 RAs, head-to-head comparisons of 5-HT_3 RAs to NK1 RAs are not available.[3-5] Similarly, the addition of olanzapine, in some settings, is also reported to improve the efficacy of regimens containing NK-1 and 5-HT_3 RAs but direct comparison with NK-1 and 5-HT_3 RAs is not available.[6]

Current guideline recommendations for CINV are highly specific to the type of chemotherapy and other factors. However, rather than favoring any one class of antiemetic, the 2020 American Society of Clinical Oncology guidelines recommend multi-drug regimens with no individual 5-HT_3 or NK1 RA agent preferred.[7]

The PONV literature includes many direct comparisons, providing the foundation for a Cochrane network meta-analysis of 585 trials with 97,516 patients. While multi-drug regimens generally outperformed single agents, among the single agents, the NK-1 RAs were found to be most effective, followed by 5-HT_3 RAs, dexamethasone, and antihistamines. Unfortunately for adverse events, the authors could only draw conclusions of low to very low certainty.[8] Guideline recommendations for PONV from the Society for Obstetric Anesthesia and Perinatology, the American Society of Colon and Rectal Surgeons, and the Society of American Gastrointestinal and Endoscopic Surgeons, while again recommending multi-drug regimens, stop short of recommending any drug classes over others.[9,10]

The generalizability of CINV and PONV findings to other settings is uncertain. For NK-1 RAs, we were unable to find studies in any other setting. For ondansetron, there are some positive data in most settings. For acute gastroenteritis in pediatric patients, a Cochrane review found only 7 studies. Ondansetron when compared with placebo reduced the risk of hospital admission (RR 0.40, 95% CI: 0.19-0.83) and IV hydration (RR 0.41, 95% CI: 0.29-0.59) and improved the likelihood of cessation of vomiting (RR 1.33, 95% CI: 1.19-1.49). In a study of ondansetron vs. metoclopramide vs. placebo, ondansetron stopped vomiting episodes in 58% of patients, metoclopramide in 33% of patients, and placebo in 17% of patients (p=0.039). In a single study, dimenhydrinate also demonstrated benefit.[11]

For adults in the Emergency Room, a Cochrane review found “no definite evidence to support the superiority of any one drug over any other drug, or the superiority of any drug over placebo”.[12]

For early pregnancy, a Cochrane review evaluated 41 randomized controlled trials (RCTs), but these were small in sample size with heterogeneous outcomes, making comparison difficult.[13] Based on these data, American and Canadian guidelines recommend pyridoxine or pyridoxine/doxylamine as first-line therapy. Interestingly, guidelines from the United Kingdom do not recommend pyridoxine but do concur with Canadian guidelines in recommending antihistamines and phenothiazines as first-line options, with ondansetron and metoclopramide serving as second-line. All three practice guidelines concur in limiting corticosteroids to refractory cases.[14-16]

For hyperemesis gravidarum, a Cochrane review of 25 RCTs found "little high-quality and consistent evidence supporting any one intervention". It did find limited evidence of a difference in side effects, namely that ondansetron caused fewer side effects than metoclopramide which, in turn caused fewer side effects than promethazine.[17]

Findings:

Aside from their enduring popularity, it is difficult to find justification for adding any of the older antiemetics to the NCF. Both the limited available evidence and practical experience suggest that their adverse event profiles are burdensome. When directly compared to 5-HT_3 or NK-1 RAs, the older antiemetic agents generally have been found to be inferior in either clinical effectiveness, side effects or both.

NK-1 RAs seem to be the most effective agents, with few side effects in the setting with the most direct comparisons available for review: PONV. Unfortunately, in clinical scenarios beyond CINV and PONV, there is a paucity even of low-quality evidence supporting NK-1 RAs, and they remain seldom used within the IHS.

Ondansetron, on the other hand, is widely used. It has, at minimum, evidence of effectiveness in most settings. While the FDA urges caution (and monitoring in certain situations) for long QTc, ondansetron is generally well tolerated. As the 5-HT_3 RAs are similar in effectiveness and side effect profile, there is little reason to include a different 5-HT_3 RA. For these reasons, ondansetron was added to the IHS National Core Formulary.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

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