Review Article

Extended release granisetron: Review of pharmacologic considerations and clinical role in the perioperative setting

ABSTRACT

In this review, we evaluate recent literature on use of ER granisetron in clinical practice as compared with current antiemetics and describe its potential uses for perioperative PONV prophylaxis and treatment. Recent literature was evaluated on ER granisetron use compared with currently used antiemetic agents ondansetron, droperidol, metoclopramide, promethazine, and dexamethasone with a focus on procedural anti-emesis. Though promising great effect, application of extended release granisetron to clinical use may be limited by it's increased relative cost.

Key words: 5-HT3 antagonists; anti-emetics; pharmacotherapy; post-operative nausea and vomiting

Introduction

Antiemetics ondansetron, metoclopramide, droperidol, promethazine, and dexamethasone are commonly used in anesthesia. Relatively safe and effective in managing postoperative nausea and vomiting (PONV), each has drawbacks and restrictions in clinical practice. Extended-release (ER) granisetron (Sustol®), a novel 5-hydroxytryptamine (5-HT_3) receptor antagonist through soft drug development received recent U.S. Drug and Food Administration approval for prevention of acute and delayed nausea and vomiting in cancer patients. Because controversy surrounding data reliability on short-acting granisetron has resolved, it has been useful in treatment of PONV.[1-6] In this review, we evaluate recent literature on use of ER granisetron in clinical practice as compared with current antiemetics and describe its potential uses for perioperative PONV prophylaxis and treatment. We performed a literature search of the Medline database (2013 - March 2017). Additional references were identified from review of literature citations, manufacturer reports, and professional meeting abstracts. Premarket studies that involved ER granisetron as the primary study drug were evaluated. Literature describing the pharmacokinetics and pharmacodynamics of the short acting granisetron (Kytril®), ondansetron, metoclopramide, droperidol, promethazine, and dexamethasone was also included. Phase I, II, and III studies in the United States have shown ER granisetron to be safe and effective for the prevention of nausea and

Access this article online	
Website: www.saudija.org	Quick Response Code
DOI: 10.4103/sja.SJA_817_18	

How to cite this article: Ngo AL, Orhurhu V, Urits I, Delfin EO, Sharma M, Jones MR, *et al*. Extended release granisetron: Review of pharmacologic considerations and clinical role in the perioperative setting. Saudi J Anaesth 2019;13:231-6.

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vomiting in cancer patients, which may be applicable to post-surgical patients. Economic analyses of costs versus benefits will need to be examined.

Materials and Methods

Recent literature was evaluated on ER granisetron use compared with currently used antiemetic agents ondansetron, droperidol, metoclopramide, promethazine, and dexamethasone with a focus on procedural anti-emesis. Medline database search was performed using the term, "extended release granisetron."Additional references were identified from a review of manufacturer reports, literature citations, and abstracts from professional meetings. All premarket studies involving granisetron as the primary study drug were evaluated. Literature describing the pharmacokinetics and pharmacodynamics of granisetron, ondansetron, droperidol, metoclopramide, promethazine, and dexamethasone were included.

Extended release granisetron

Developed as APF530 by A.P. Pharma (now Heron Therapeutics), ER granisetron received regluatory approval in August 2016 under trade name Sustol® for treatment in acute and delayed phase of chemotherapy induced nausea and vomiting (CINV).[7] It has experienced successful adoption as a delayed-release antiemetic.[8] With increased durability of effect, ER granisetron has potential for future use in PONV.

Mechanism, pharmacokinetics, pharmacodynamics, and efficacy

Granisetron selectively binds and antagonizes 5-HT_3 receptors to prevent serotonin mediated emetogenic stimuli. ER granisetron demonstrates favorable bio-parameters, including slow hydrolysis with plasma detection for 7 days with maximum plasma concentration at 24 h following single dose. Dosing frequency is maximized at once per week.[9] Composed of 2% granisetron and a bioerodible tri (ethylene glycol) poly (orthoester) polymer, drug delivery is sustained release with a terminal elimination half-life of 24 h and predominantly cleared through hepatic metabolism.[10]

ER granisetron appears to be superior to ondansetron. In phase 3 studies, ER granisetron treated group experienced a greater complete response (CR) rate (65%) compared to IV ondansetron (56%; $P = 0.014$) in the delayed phase onset phase of CINV (24-120 h post HEC) with better secondary endpoints including delayed complete control (CC), overall CR, overall CC, and overall no emesis. In addition, ER granisetron showed a comparable safety and tolerability profile compared to ondansetron.[11] As an antiemetic, the increasing durability of therapeutic efficacy from granisetron and a competitive safety and tolerability against commonly used antiemetics make it well-suited for potential use beyond chemotherapy. The findings of clinical trials assessing safety and efficacy of ER granisetron are summarized in Table 1.

Use in procedures as a prophylactic and therapeutic antiemetic

ER granisetron can be useful in clinical anesthesia. In procedures for patients with known severe nausea and vomiting, it can decrease morbidity and mortality in medical conditions where PONV would exacerbate complications.

One potential area for use of ER granisetron is pregnancy, especially in patients with hyperemesis gravidarum and cesarean delivery patients under general or neuraxial anesthesia. In a double blinded randomized controlled trial (RCT), short-acting granisetron showed a reduced PONV incidence of 25% in the granisetron group versus 62.5% in placebo.[12] Compared to ondansetron, which is commonly used in pregnant patients, granisetron presents with similar efficacy, but potency and duration are far superior. Hyperemesis gravidarum has been traditionally treated with promethazine and ondansetron.[13] Limited safety data exist for 5-HT_3 receptor antagonists in pregnancy, given the popular use of ondansetron. In a double blind randomized RCT assessing efficacy and incidence of adverse reactions for managing hyperemesis gravidarum, granisetron was superior to promethazine with patients receiving granisetron experiencing fewer vomiting episodes at 48 h, shorter hospital stays, lower rates of rehospitalization, and no reported adverse drug reactions.[14] An ER formulation could benefit this patient population with less frequent dosing, especially in those with a known history of nausea and vomiting.

ER granisetron can be used in surgical patients with a high incidence of PONV such as abdominal, gynecologic, laparoscopic, breast, and ENT surgery. Granisetron has been shown to be effective as prophylactic anti-emetic therapy in these populations. One study showed granisetron was more efficacious than droperidol in preventing PONV during the first 24 h following surgery (incidence of PONV 22% vs. 42%).[15] Overall, surgical patients with high risk for prolonged PONV or known history, may find ER granisetron to be effective and better tolerated, reducing post-operative recovery, and unexpected medical visits.

Further development and potential for clinical use

Since FDA approval, ER granisetron has been used in patients undergoing cytotoxic chemotherapeutic therapy. However recently, granisetron has been described as a treatment for pain given serotonin's role in pain pathways.

Table 1: Summary of extended release granisetron trial data

Clinical Trial	Treatment Groups	Results
Phase 3 (Magic)	APF530 500 mg + Fosaprepitant + Dexamethasone + Ondansetron; following single-day AC based HEC APF530 500 mg (placebo) + Fosaprepitant + Dexamethasone + Ondansetron; following single-day AC based HEC	Although statistical significance was not reached, numerical benefit was observed with APF530 compared to ondansetron for complete and total responses, particularly in overall and delayed phases of CINV
Phase 3 (non-inferiority)	APF530 10 mg + Dexamethasone Palonosetron 0.25 mg + Dexamethasone	APF530 demonstrated non-inferiority in acute and delayed phases of CINV compared to palonosetron
Phase 2	APF530 (250 mg, 500 mg, 750 mg; 5 mg, 10 mg, 15 mg granisetron respectively in patients simultaneously receiving MEC or HEC	Dose proportional pharmacokinetic profile with slow release after a single subcutaneous APF530 injection. Minimal differences between 250 mg and 500 mg APF530 dose; 250 mg and 500 mg doses proceeded to pivotal studies
Phase 1	APF530 (125 mg, 250 mg, 500 mg, and 1 g) Granisetron IV (7 days post APF530) Placebo	Safety profile similar to IV granisetron, with dose proportional pharmacokinetic parameters and bioavailability at all doses. Absorption was prolonged with respect to intravenous granisetron

In a double blind RCT, patients treated with repeated intramuscular tender-point injections with granisetron for pain of temporomandibular regions demonstrated a 40% decrease in pain versus control at 1 month and 55% decrease at 6 months.[16] Further studies may elucidate a role for granisetron in many generalized pain syndromes, where ER granisetron may help in pain control with infrequent outpatient dosing.

Safety concerns

A major safety concern exists for 5-HT_3 antagonists, namely QT_c interval prolongation causing serious arrhythmias and subsequently death. The FDA has issued a warning for this drug class regarding these potential cardiac effects. Granisetron has not been found to have any significant effects on QT_c interval in clinical trials.[15,17,18] However, limited information is available in regard to ER granisetron, and more studies are needed to address potential safety concerns.

Discussion

The effective management of PONV is important in perioperative care. In some studies, PONV is often rated as worse than postoperative pain by patients.[19] PONV can affect patient satisfaction, impact traditional outcome variables, including hospital length of stay and readmission rates, and results in complications such as dehydration, aspiration, wound dehiscence, and secondary complications such as esophageal rupture or pneumothorax.[20] PONV is common-without prophylaxis, it is reported to occur in 30% to 80% of patients.[21] Serotonin (5-HT_3) receptor antagonists are the current standard for PONV and are relatively safe and efficacious.[22] They lack sedative side effects, as compared to the other PONV drugs that act as antagonists for dopamine D2 receptors in the chemoreceptor trigger zone in the area postrema of the medulla.[23] This is an important advantage postoperatively, which is why some clinicians reserve these drugs for post-anesthesia care. ER granisetron, another 5-HT_3 receptor antagonist, was FDA-approved in 2016 for acute and delayed nausea and vomiting in cancer patients.[24] This is a high-risk group, and given its efficacy for CINV, it may prove useful in PONV.

In current regimen, 10 mg of ER granisetron injected subcutaneously versus intravenous administration with other antiemetics has important implications in nursing resource utilization.[9] Its slow release over 7 days with a peak concentration in plasma 24 h after injection makes it a viable candidate to treat PONV, while at the same time, addressing drawbacks of regular-release granisetron (Kytril®), which is short-acting, has a half-life of 6 h, and possesses a narrow therapeutic index.[9] The ability of extended release granisetron to maintain therapeutic drug levels for 5 days with a single subcutaneous injection provides a high convenience factor for staffing and costs reduction.[25] However, this benefit addresses not only acute phase postoperatively but also has potential impact on readmission rates, which is particularly important in surgeries associated with high PONV predictive scores. Many surgeries, such as laparoscopic cholecystectomy, gynecologic surgeries, and tympanoplasty, are increasingly performed in the same day surgery centers or on in-patients with rapid discharge planning, where most benefit can be achieved.

Granisetron, as an antiemetic drug, demonstrates favorable efficacy and fewer side effects. As a selective 5-HT_3 antagonist, antiemetic effects are achieved by blocking vagus nerve 5-HT receptors without affinity for other 5-HT receptors. Although major antiemetics used in PONV are more effective than placebo, 5-HT_3 antagonists were more effective in meta-analysis in children compared to metoclopramide and droperidol.[26,27] Furthermore, 5-HT_3 antagonists were far less

likely to cause extrapyramidal side effects (metoclopramide), sedation (phenothiazines, butyrophenones - droperidol), or QT_c prolongation (droperidol).[28,29] This makes using granisetron easier when considering patients with polypharmacy who may be taking other drugs known to prolong the QT_c interval (anti-depressants, anti-psychotics, antihistamines, and some antibiotics such as the macrolides and quinolones). Although prokinetic effects of metoclopramide are effective in pregnancy, extrapyramidal side effects are deleterious in higher doses.[30] In addition, combination therapy for high-risk patients with PONV is more effective than monotherapy, and in this scenario, using extended release granisetron as the 5-HT_3 antagonist with phenothiazine may allow coverage beyond the early postoperative phase while avoiding delayed sedation.[29] Further, subcutaneous ER granisetron use will avoid severe tissue injury associated with accidental promethazine extravasation. Although dexamethasone was found to be as effective as others therapies, including tropisetron and ramosetron, consideration must be made of the risk and benefits in diabetics, pregnant patients, and those prone to anxiety and gastric ulceration.[31]

ER granisetron may play a role in enhancing efficiency and better care in organizations. Institutional policies consider safety, efficacy, ease of ordering, administration, and patient satisfaction when generating standards of care and algorithms in care pathways. When ER granisetron was compared to gold standard antiemetics, specifically ondansetron, it had similar if not better safety and tolerability profiles. The added advantage of delayed release antiemetic effect (avoiding the narrow therapeutic index of granisetron) and durability of effect makes it very attractive when considering early discharge and avoiding readmission.[32] Most organizations have algorithms for prophylaxis of PONV, a reportable quality measure to CMS with possible punitive consequences for Medicare reimbursement. Droperidol, promethazine, and metoclopramide have side effects including headache, sedation, drowsiness, fatigue, and extrapyramidal symptoms. In addition, droperidol, as mentioned above, had an FDA-issued warning about arrhythmias and deaths from QT_c interval prolongation. Promethazine also cannot be given to patients with neurological, cardiac, or respiratory depression, and the FDA issued a black box warning for it causing gangrene or severe tissue injury if leaked into local tissues.Side effects of dexamethasone include anxiety, insomnia, psychosis, and gastric ulcers.[31] Overall, side effect profiles of 5-HT_3 antagonists are less.[27]

Currently, ondansetron is the standard. However, ER granisetron, being in the same class, has a similar efficacy, but is more potent, has a longer duration, and is possibly better in safety because of greater selective 5-HT_3 antagonism.[15] In addition, potential side effects of ondansetron include headache, malaise, constipation, and diarrhea with the most harmful being cardiac arrhythmias and death. ER granisetron, however, has shown not to cause electrocardiogram (ECG) changes, only yielding side effects of constipation, diarrhea, dyspepsia, abdominal pain, and headache.[33] Ondansetron is useful as prophylaxis, but granisetron is more potent, longer-acting, making it potentially more useful in those patients with a known PONV history or refractory PONV.[4]

When compared with dexamethasone, ER granisetron presents strong merits for use. Dexamethasone, used for PONV prophylaxis, is effective in immediate as well as initial postoperative period.[34] However, dexamethasone may cause glycemic disturbances in diabetics, anxiety/insomnia in elderly, and impact those on psychiatric medications, making ER granisetron more attractive in patients with multiple comorbidities.[31] The single injection model of ER granisetron could ensure better compliance and safety in cognitively impaired elderly. In the "early discharge" paradigms, ER granisetron may have advantages over phenothiazines and dexamethasone, given less sedation and perturbation of glycemic control, respectively.[28]

ER granisetron presents usability in multiple clinical settings. In ICU, ER granisetron may have advantages in avoiding QT_c prolongation with polypharmacy, especially with other drugs that may be contraindicated in cardiac patients.[33] It can be used in outpatient settings, such as clinics or for elderly nursing homes because ER granisetron is subcutaneously injected rather than intravenously given. Results have shown that ER granisetron to be safe and efficacious in certain patients such as pregnant women.[14] Its potency and efficacy needs to be compared to newer generation 5-HT_3 antagonists such as palonosetron, also approved for CINV, but is more expensive than ER granisetron (granisetron costs $23.36 per 3 mg, whereas palonosetron costs $118 for 0.75 mg).[25] However, ER granisetron may have unknown effects such as desensitization or rebound phenomena because of its prolonged nature.[4] Further safety and efficacy studies are needed to investigate potential long-term effects.

The relatively good safety profile and selectivity of granisetron as a 5-HT_3 antagonist may make it appealing for other clinical indications. Most promising is chronic pain management through local injection in pain areas.

Conclusion

ER granisetron is a recent anti-emetic agent to arise out of soft drug development. It has a potential as a valuable

adjunctive anti-emetic agent. It has received FDA approval for market in 2016 as an antiemetic for CINV with the potential to be used in the perioperative setting. More studies must be conducted to compare the efficacy of ER granisetron on reducing nausea and vomiting in relation to commonly used drugs today. Although promising great effect, application to clinical use may be limited by increased relative cost.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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