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The Use of 5-HT_3 Antagonists in the Prevention of Nausea and Vomiting in Children

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Selective serotonin 5-hydroxytryptamine (5-HT_3) receptor antagonists have been in use in the United States for nearly a decade. This therapeutic class has revolutionized the prevention of nausea and vomiting in patients receiving chemotherapy or radiation and is now gaining a foothold in the perioperative setting.

There are currently two 5-HT_3 antagonists available in the United States, ondansetron (Zofran®) and granisetron (Kytril®). A third agent, dolasetron is currently available in Europe and is expected to be approved for use in the United States within the next year.[1-6]

Mechanism of Action

Antagonism by these agents at the 5-HT_3 receptor prevents binding of serotonin both peripherally at vagus nerve terminals and centrally in the chemoreceptor trigger zone. The 5-HT_3 antagonists are highly selective, with little or no affinity for other serotonin, alpha or beta-adrenergic, or dopamine receptors.[1-6]

Use in Children

Both ondansetron and granisetron are FDA-approved for use in children.[2,3] They have been studied extensively in children receiving chemotherapy.[7-11,18-23] Newer reports have focused on their role in preventing nausea and vomiting in children receiving radiation, undergoing bone marrow or stem cell transplantation, and having surgery.[12-17,23,24]

The efficacy and safety of ondansetron in pediatric cancer patients has been established through many clinical trials. Most of these studies have demonstrated efficacy rates of 60 to 93% in the prevention of significant nausea or emesis, similar to rates reported in adults. This rate of efficacy is much greater than that of other therapies.[7-16] As an example, a comparison trial of ondansetron versus the combination of metoclopramide with dexamethasone conducted in children receiving cytarabine, etoposide, and daunorubicin revealed a dramatic difference. A full or major response (two or less episodes of vomiting) was achieved in 93% of the ondansetron-treated children, but only 33% of children receiving the combination.[14]

In the past three years, several reports of granisetron use in children have been published. A similar rate of efficacy to ondansetron has been documented, with a range of 68 to 87% of pediatric patients having a full or major response following prophylactic use prior to chemotherapy.[18-22]

Ondansetron and granisetron have also been studied in combination with dexamethasone in children receiving chemotherapy. Similar to studies conducted in adults, the use of this combination improves efficacy. Alvarez et al[13] studied 33 children receiving highly emetogenic chemotherapy. The study was randomized, with a double-blinded crossover design. The combination group received 0.15 mg/kg ondansetron with 8 mg/m^2 dexamethasone 30 minutes prior to being given chemotherapy. The control group received just the ondansetron dose. When complete and major responses were combined, the combination regimen achieved success in 86% of the children compared to 67% with ondansetron alone.

The use of 5-HT_3 antagonists in the prevention and treatment of postoperative nausea and vomiting in children has also been studied.[17,23,24] Davis and colleagues[17] compared the efficacy of a single dose of 0.1 mg/kg ondansetron to 75 mcg/kg droperidol or placebo in a double-

blinded study of 95 children undergoing general anesthesia for dental restoration. At 24 hours post-surgery, the incidence of emesis was significantly less with ondansetron (9%) compared to droperidol (32%) or placebo (35%). The ondansetron-treated patients also had an overall shorter length of hospitalization. Similar rates of efficacy have been shown with granisetron, using 20 to 40 mcg/kg as a single dose.[23,24]

Adverse Effects

Unlike other antiemetics, such as benzodiazepines or phenothiazines, the 5-HT_3 antagonists are relatively free of adverse effects. For example, extrapyramidal symptoms are much less likely to occur with the selective 5-HT_3 antagonists than with antiemetics which also bind to dopamine D_2 receptors, such as metoclopramide. Specificity for 5-HT_3 receptors, however, is greater with granisetron than ondansetron. Granisetron has only rarely been associated with extrapyramidal symptoms, while clinical trials with ondansetron have shown an overall incidence of extrapyramidal symptoms to be approximately 6%.[4]

The most frequently reported adverse effects with ondansetron and granisetron are headache (10 to 20%), and constipation or diarrhea (5 to 18%). Constipation occurs approximately twice as often as diarrhea in patients treated with granisetron. Ondansetron causes these effects in nearly equal numbers. Subjects receiving ondansetron in clinical trials have also reported a 5 to 10% incidence of agitation, dizziness, fever, malaise/fatigue, and sedation. Subjects given granisetron have reported asthenia (incidence approximately 10 to 15%).[2,3] In pediatric trials, adverse effects appear relatively rare, with most reporting only sedation and mild headache.[12,13,19,22]

There are rare reports of seizures, changes in blood pressure (both hyper- and hypotension), arrhythmias, anemia, thrombocytopenia, and hypersensitivity reactions following ondansetron or granisetron use.[2,3]

Drug Interactions

At this time, there have been no significant drug interactions documented with the 5-HT_3 antagonists. Since these agents are metabolized via the cytochrome P450 enzyme system, the 5-HT_3 antagonists are affected by inducers or inhibitors of the P450 system, resulting in a change in elimination half-life. However, these reactions do not appear to be clinically significant and there are no recommendations for dosage adjustment based on drug interactions.[2,3]

Dosing Recommendations

Ondansetron is available in injectable form (2 mg/ml), as well as tablets (4 and 8 mg) and an oral solution (4 mg/5 ml). Pediatric patients should receive an intravenous or oral dose of 0.15 mg/kg administered 30 minutes prior to chemotherapy, radiation therapy, or immediately prior to surgery. Intravenous ondansetron should be given over 15 minutes.[1,2] A second and third dose should be administered at 4 hour intervals if needed.

Granisetron is available in injectable form (1 mg/ml) and 1 mg tablets. An oral suspension may be compounded from the tablets for younger children or patients unable to swallow tablets.[25] Pediatric patients should be given an oral or intravenous dose of 10 to 20 mcg/kg 30 minutes prior to treatment or immediately before surgery. Higher doses of up to 40 mcg/kg have also been used. Intravenous granisetron should be infused over 5 minutes.[1,3]

The issue of appropriate dosing intervals for continued therapy continues to be studied. Ondansetron has been administered at intervals from every 4 to 12 hours.[12,15,26,27] Granisetron is typically administered once daily. Many pediatric institutions have developed guidelines for the use of these drugs according to indication and likelihood for emesis. An evaluation of dosing requirements is currently underway at the Children's Medical Center.

Medication Compatibility

In children with cancer, there is often a need to infuse numerous medications simultaneously, due to limited intravenous access and the desire to minimize treatment time. As a result, the compatibility of the 5-HT_3 antagonists has been studied with a variety of other intravenous medications.[28-32]

The following table provides an abbreviated list of medication compatibility information for agents commonly used in the treatment of children with cancer. For further information, please refer to the publications by Trissel and Mayron.[28-32]

Table. Examples of 5-HT_3 Antagonist Compatibility[a]

Medication	*Ondansetron*	*Granisetron*
Acyclovir	N	Y
Allopurinol	N	Y
Amphotericin	N	N
Ampicillin	N	Y

Aztreonam	Y	Y
Bleomycin	Y	Y
Carboplatin	Y	Y
Carmustine	Y	Y
Cefotaxime	Y	Y
Ceftazidime	Y	Y
Chlorpromazine	Y	Y
Cisplatin	Y	Y
Cyclophosphamide	A, Y	Y
Cytarabine	Y	Y
Dactinomycin	Y	Y
Dexamethasone	A, Y	Y
Diphenhydramine	Y	Y
Doxorubicin	Y	N
Etoposide	Y	Y
Filgrastim	Y	Y
Fluconazole	A, Y	NA
Fluorouracil	N	Y
Furosemide	N	Y
Hydrocortisone	Y	Y
Ifosfamide	Y	Y
Lorazepam	N	Y
Mesna	Y	Y
Methotrexate	Y	Y
Methylprednisolone	N	Y
Metoclopramide	Y	Y
Morphine	A,Y	Y
Potassium chloride	Y	Y
Prochlorperazine	Y	Y
Promethazine	Y	Y
Ranitidine	A,Y	Y
Sodium Bicarbonate	N	Y
Vancomycin	Y	Y
Vincristine	Y	Y

[a] A= additive compatibility; Y= compatible at Y-site; N = not compatible; NA = no information available

Cost of Therapy

The primary disadvantage to using the 5-HT_3 antagonists is their cost. The acquisition cost for intravenous therapy at the Children's Medical Center is approximately $50 to $100 per dose. The cost for oral therapy is approximately one third of the intravenous cost.

Individual doses of ondansetron are less expensive than granisetron; but since ondansetron is dosed more frequently, it usually becomes the more expensive therapy. Standardization of dosing to allow recycling of unused doses and reducing the frequency of dose administration are methods being used in the Children's Medical Center to reduce costs.

Summary

The 5-HT_3 antagonists offer a unique alternative to other antiemetic therapies. They offer a high rate of efficacy with relatively few adverse effects or drug interactions. Their primary disadvantage remains cost. Appropriate use and reduction of drug waste are important to make full use of this therapy.

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FDA Update

The issue of mandatory pediatric labeling of medications has been revisited by the Food and Drug Administration (FDA). In an effort to clarify previous regulations, the FDA has announced that requirements for pediatric studies will apply only to medications submitted as new molecular entities. As a result, manufacturers will be required to submit pediatric data for only one indication. Additional "off-label" uses would still be permitted, but manufacturers would not be mandated to study each possible use in children.

Medications already available would still be required to have pediatric labeling added if the product is widely used in children or is used for a life-threatening illness when additional information is needed to allow safe use in children. As an example, the FDA has cited the lack of labeling information on albuterol in children under 12 years of age. Pharmaceutical manufacturers may apply for a waiver if their product does not represent a significant benefit over existing therapies or if it will not be widely used in the pediatric population. A waiver may be general or apply only to a subgroup of children, such as neonates.

To pediatric health care providers, these new regulations will result in the availability of more clinical trial data on which to base treatment decisions. These changes may also bring about new issues, including direct-to-consumer advertising of pediatric medications.

Pharmacology Literature Review

Acellular Pertussis Review

This review highlights the transition from whole cell pertussis vaccine to the newer acellular products. The article focuses on the efficacy of the new products, in terms of reactivity, immunogenicity, and clinical response. A brief overview of pertussis and the development of both whole cell and acellular vaccines are also provided. Lopez AL, Blumberg DA. An overview of the status of acellular pertussis vaccines in practice. **Drugs 1997;54:189-96.**

Scientific Bias Against Negative Results

This editorial, from one of the leading researchers in the area of maternal-fetal pharmacology, addresses the controversy related to studies assessing risk of teratogen exposure. The author suggests that studies reporting no adverse fetal effects following maternal exposure to a substance are less likely to be accepted for presentation or publication than those demonstrating adverse outcomes. As a result, patients may receive unbalanced medical information, which may lead to unwarranted alarm. Koren G. Bias against the null hypothesis in maternal-fetal pharmacology and toxicology. **Clin Pharmacol Ther 1997;62:1-5.**

Vancomycin Review

The results of numerous vancomycin pharmacokinetic studies in infants and children are reviewed in this article. The authors provide a detailed analysis of dosing recommendations based on these studies and address the issues of differences in methodology and the needs of special populations, such as burns or cancer. Rodvold KA, Everett JA, Pryka RD et al. Pharmacokinetics and administration regimens of vancomycin in neonates, infants and children. **Clin Pharmacokinet 1997;33:32-51.**

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