DERLEME

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Evaluation of Antiemetic Therapy Used for Chemotherapy Induced Nausea and Vomiting in Children

Çocuklarda Kemoterapiye Bağlı Bulantı ve Kusma için Kullanılan Antiemetik Tedavinin Değerlendirilmesi

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SUMMARY

Nausea and vomiting associated with chemotherapy is one of the important side effects of treatment in children with cancer. Despite the development of new antiemetic agents, there are still some problems in this regard in children. The combination of a 5-HT3 receptor antagonist plus a corticosteroid is usually used to prevent chemotherapy induced nausea and vomiting (CINV) in children receiving emetogenic chemotherapy. New antiemetic agents do not take part in the current pediatric guidelines. There is also no sufficient data on alternative agents in children with intractable vomiting. This review summarizes the CINV definitions in children, the classification of the antiemetic drugs as standard, newly available and optional drugs in children. Each drug category is discussed according to the mode of action, efficacy in different types of CINV, recommended dose and finally some suggestions for CINV in children.

Key words: Nausea, vomiting, chemotherapy, children, antiemetic agents

ÖZ

Kemoterapiyle ilişkili bulantı ve kusma, kanserli çocuklarda tedavinin önemli yan etkilerinden birisidir. Yeni antiemetik ajanlar gelişmiş olmasına ragmen çocukluk yaş grubunda halen bazı sorunlar vardır. Çocuklarda kemoterapiye bağlı bulantı ve kusmayı önlemek için genellikle bir 5-HT3 reseptor antagonisti ile kortikosteroid birlikte kullanımı önerilir. Yeni antiemetik ilaçlar güncel pediatri kılavuzlarında yer almazlar. Dirençli kusması olan çocuklarda alternatif ajanların kullanımına ilişkin yeterli veri yoktur. Bu derlemede; çocuklarda kemoterapiye bağlı bulantı kusma ile ilgili tanımlar, çocuklarda kullanılan antiemetik ilaçların standart ilaçlar, isteğe bağlı ilaçlar ve yeni ilaçlar olarak sınıflandırılması özetlenmiştir. Her ilaç kategorisi, etki mekanizması, dozları ve çocuklarda antiemetik tedaviyle ilgili bazı öneriler tartışılmıştır.

Anahtar Kelimeler: Bulantı, kusma, kemoterapi, çocuklar, antiemetik ajanlar

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Introduction

Chemotherapy induced nausea and vomiting (CINV) is one of the most common complaints in children with cancer. It affects the children's quality of life. CINV can cause some significant medical problems such as dehydration and electrolyte imbalances, increased duration of hospital stay (1,2). CINV may also compromise their compliance with chemotherapy schedule. Children are more sensitive to vomiting compared to adults. Some emotional and psychological factors are also get involved in children. Despite recent important developments in antiemetic therapy, some problems are going on in children receiving emetogenic chemotherapy. Current standard recommendation in children with cancer is the use of a 5-hydroxytryptamine 3 (5-HT-3) receptor antagonist plus a corticosteroid to prevent emesis (3,4). Despite this treatment, over than 40% of patients still report the complaint of nausea and vomiting after highly emetogenic chemotherapy. Alternative antiemetic agents in children with inadequate response are controversial. Most of the current literature is related to the adult patients (5,6).

This review summarizes the CINV definitions in children, the classification of the antiemetic drugs as standard, newly available and optional drugs in children and finally some conclusions for CINV in children. Each drug category is discussed according to the mode of action, efficacy in different types of CINV, recommended doses in children.

1. CINV definitions: There are three CINV definitions which can be classified according to onset. Acute CINV starts within 24 hours after the treatment. Nausea and vomiting observed 24 hour after chemotherapy is called as delayed emesis. The prevention of delayed emesis is the most important in patients receiving cisplatin containing regimen. Delayed CINV is observed in 20-80% of patients and lasts 2-7 days. (6). The last type is anticipatory CINV indicating that symptoms appear before chemotherapy administration. It is also called psychological CINV and observed in 25% of children receiving chemotherapy. It occurs due to previous chemotherapy experience as a conditioned response (7).

2. Pharmacological Treatment for CINV in children: Several drugs have been available for treatment and prevention of CINV. The mod of action of these antiemetic drugs is associated with emesis pathophysiology. Emesis is managed by the emetic center in the central nervous system. The lateral reticular formation of medulla is the location of emetic center. This area is known as "chemoreceptor trigger zone". The impulses coming from various areas such as chemoreceptor trigger zone, brain cortex, and peripheral afferent fibers from the gastrointestinal tract affect the emetic center. Thereby, the emetic center regulates the activation of somatic and visceral efferent fibers directed to the effector organs including abdominal muscles, stomach, esophagus and diaphragm. There are many different types of receptors associated with CINV such as 5-hydroxytriptamine (5-HT2, 5-HT3, 5-HT4),

dopamine receptors (D2), histamine receptors (H1), acetylcholine receptors (Ach), and NK1 (neurokinin 1) receptors. Antiemetic drugs show their action by affecting these receptors.

The central and the peripheral mechanisms are both major mechanisms which emesis is controlled. After exposure to chemotherapy or radiotherapy, serotonin is released in small bowel mucosa and binds to the 5-HT3 receptors located on vagal afferent abdominal neurons. And the emetic response starts by activating fibers.

The selection of antiemetic drugs is associated with presence of risk factors which depend on patients and treatment. Patient factors are female sex, age>3 years, anxiety, motion sickness and inadequate symptom control in a previous cycle of chemotherapy (8).The emetogenic potential of chemotherapeutic drugs is a treatment related risk factor. Antineoplastic drugs are firstly classified according to the emetogenic potential by Hesketh et al.(9). This classification has been revised and published in 2008 (Table1)

Table 1. Chemotherapeutic drugs classified according to the risk of emesis

High Risk in nearly all patients (>90%)	Cisplatin, Mechlorethamine Cyclophosphamide>1500 mg/m2 Carmustine, Dakarbazine, streptozocin
Moderate Risk in 30% to 90%of patients	Oxaliplatin, Cytarabine>1000 mg/m2 Carboplatin, Ifosfamide, Irinotecan Cyclophosphamide, Doxorubicine Daunorubicine, Epirubicine, Idarubicine
Low Risk in 10% to 30%of patients	Paclitaxel, Docetaxel, Mitoxantrone Topotecan, Etoposide, Pemetrexed Methotrexate, Mitomycine, Gemcitabine Cytarabine <100 mg/m2, 5-Fluorouracil Bortezomib, Cetuximab, Transtuzumab
Minimal Risk in fewer than 10% of patients	Bleomycin, Busulfan 2-Chlorodeoxyadenosine, Fludarabine Vinblastin, Vincristin Vinorelbine, Bevacizumab

Modified from: Multinational Association of Supportive Care in Cancer (MASCC), Antiemetic guidelines- 2008.

There are some antiemetic therapy recommendations for CINV enhanced by the Multinational Association of Supportive Care in Cancer (MASCC) and American Society of Clinical Oncoloy (ASCO) (3). The information of the most effective antiemetic therapy to prevent chemotherapy induced nausea and vomiting is limited in children, the combination of a 5HT-3 receptor antagonist with a corticosteroid

is the most commonly prescribed treatment for chemotherapy induced emesis in children with cancer, particularly in children receiving highly emetogenic chemotherapy (Table 2) .

Table 2. Current recommendations for CINV in children

Emetogenic Potential	Acute	Delayed
High	5-HT3 +dexamethasone	5-HT3 +dexamethasone or metoclopramide
Moderate	5-HT3	Dexamethasone alone or 5-HT3 + dexamethasone
Low	Single agent (5-HT3 or dexamethasone)	none

No clear recommendation is possible for children who are failed after use of 5HT3 receptor antagonist and dexamethasone. Antiemetic agents that are used in adult patients with cancer are not included in the current pediatric guidelines. There are barriers to adherence to the exist pediatric guidelines for antiemetic choices in children receiving chemotherapy (10-11). It is valuable to classify the antiemetic drugs as three main groups: standard drugs, newly available drugs, and optional drugs.

A. Standard drugs

a) Dopamine Antagonists: Metoclopramide, chlorpromazine and prochlorperazine take place in this group. Metoclopramide is one of the dopamine antagonists widely used. Its effectiveness in children has been demonstrated by several studies. They are effective in inhibiting emetic center induced by peripheral impulses. The recommended dose in children ranges 1-3 mg/kg/dosage. They prevent CINV in 40% of cases(12). The restricted antiemetic activity and side effects in children have caused the limitation of its use in children. Extrapyramidal reactions, diarrhea and drowsiness are side effects of this group. The dose of chlorpromazine for CINV in children has been reported at doses ranged from 0.3 to 1 mg/kg every 3-6 hours.

Similarly, the use of phenothiazines and butyrophenones is also limited to the treatment for low emetogenic chemotherapy because of extrapyramidal side effects(12). They can lead commonly major extrapyramidal reactions such as dystonia, oculogyric crisis at high doses.

b) 5- Hydroxytryptamine (5-HT3) receptor antagonists: In this group, ondansetron, granisetron, tropisetron, dolasetron and palonosetron, all of them, inhibit the binding of serotonin to type 3 receptors. In children, these group antiemetics are more effective than dopamine antagonists in controlling acute CINV.

Although the data regarding the optimal oral and intravenous doses of the 5-HT3 receptor antagonists in children are few, recommended doses for ondansetron are 5 mg/m2 or 0, 15 mg/kg every 8 hours and for granisetron 0.01-0.04 mg/kg once day (10,11).

Palonosetron , a second generation 5-HT3 receptor antagonist, has substantially longer elimination half life and a greater affinity for the 5-HT3 receptor. It has been reported to be more powerful than first generation drugs in adult patients. The data regarding use of palonosetron in children is limited, yet. The use of 5-HT3 receptor antagonists is generally safe in children. They may cause some electrocardiographic changes. But, these changes are not important clinically (13). Complete protection has been provided by the addition of steroids in about 90% of patients. Current standard recommendation in children with cancer is the use of a 5-hydroxytryptamine 3 (5-HT-3) receptor antagonist plus a corticosteroid to prevent emesis for highly emetogenic chemotherapy.

c) Corticosteroids: Corticosteroids are more effective antiemetics in CINV than chlorpromazine or metoclopramide. Dexamethasone is generally preferred for prevention of acute and late CINV in children. Their antiemetic effect is due to many mechanisms. Decreasing chemotherapy related serotonin release, alteration of blood-brain barrier are some of these mechanisms. The use of dexamethasone alone can provide good protection in most patients. Doses for dexamethasone range from 6 mg to 24 mg/m2 day. It is especially useful when administered in combination with 5-HT3 serotonin receptor antagonists in patients receiving high emetogenic chemotherapy. It has been found to increase the effects of 5-HT3 receptor antagonists in CINV(14). They ensure good impact in low or moderate emetogenic chemotherapy. When they are used in combination with other emetogenic drugs such as 5-HT3 receptor antagonists, they show the great effectiveness in preventing CINV.

But, there are some fears about the use of dexamethasone in the treatment of brain tumors. Some reports have reported that corticosteroids may reduce the moving of chemotherapy into the tumor(2). Therefore, some pediatric brain tumor trials do not recommend the use of steroids as an antiemetic.

B. Newly available drugs

a. Neurokinin-1 (NK-1) receptor antagonists (aprepitant): Aprepitant, a new antiemetic drug, antagonizes substance P effects by binding to NK-1 receptors. Aprepitant improves acute CINV control when used in combination with 5HT3 receptor antagonist and steroids in adult patients. Current guidelines recommend the use of aprepitant in CINV in adults. The experience with aprepitant in children is not much (15). There is a limited data regarding pediatric dosing and safety. Recently, Kang et al. published a randomized, phase 3 study in children aged 6 months to 17 years related to use of aprepitant (16). It has been reported that children receiving highly emetogenic chemotherapy were randomly given an age and weight based regimen of aprepitant. They used aprepitant in the following doses: 125 mg for ages 12-17 years; 3 mg/kg up to 125 mg for ages 6 months to <12 years) plus ondansetron on day 1, followed by aprepitant 80 mg for ages 12-17 years; 2 mg/kg up to 80 mg for ages

6 months to >12 years.) on days 2-3. or placebo plus ondansetron. They reported that addition of aprepitant to ondansetron is effective for prevention of chemotherapy induced nausea and vomiting in children (16). Before aprepitant is included standard antiemetic selection in children, further studies must be done.

C. Optional drugs

a. Benzodiazepines: Various different types of antiemetic agents can be used together in order to increase antiemetic efficacy and decrease associated toxicity. Sedating a patient may be useful in cases of refractory emesis. Benzodiazepines improve comfort and decrease anxiety in adult patients. Midazolam, short acting benzodiazepine, has been demonstrated to improve antiemetic effect for prolonged postoperative emesis. Reducing anxiety and causing sedation.are important in preventing CINV . Midazolam, a short-acting benzodiazepine, has been studied in treating CINV in adult patients and demonstrated that it caused a decrease in CINV(17,18). Contrary, the effectivity could not be shown in our previous study. We reported that antiemetic cocktail including midazolam was not superior to the granisetron plus dexamethasone combination in controlling emesis in acute and delayed phase(19).

b. Olanzapine: Olanzapine, an atypical antipsychotic agent, is effective on many receptors that are important in the mediation of CINV, including dopamine, serotonin, and histamine receptors. Several adult studies showed the antiemetic efficacy in CINV. Recently, Flank et al. reported that olanzapine was used in sixty children and may be an important option to improve CINV control (20). It was given at doses 0,10-0.05 mg/kg/dose. Olanzapine use can be considered in children after further clinical trials.

Conclusions: Chemotherapy induced nausea and vomiting is still an important problem in children receiving chemotherapy. It is a complex condition that has also psychological and emotional aspects in pediatric patients.

- The lack of a well-designed guideline for antiemetic therapy is one of the major challenges in children. In antiemetic guidelines published by MASCC, very little attention has been given to the problem of CINV in children.

- The current pediatric guideline recommends that a combination of a 5-HT3 receptor antagonist and dexamethasone should be given to all children for moderate or highly emetogenic chemotherapy. The most of the patients will respond completely with this combination. A small number of patients will require alternative regimens. There are no need prophylactic antiemetics for low and minimal emetogenic chemotherapy. Single antiemetic agent is usually enough for low or moderate emetogenic chemotherapy

- There is no data to recommend the choices of alternative antiemetic drugs for pediatric cancer patients who do not respond sufficiently to the standard antiemetic therapy.

- It is not accurate to reflect that adult data can be completely implemented to children, since drug metabolism and side effects may be quite different in children. New antiemetic agents such as neurokinin 1 receptor inhibitor, aprepitant, have been reported to improve control of emesis in adults. But it is still not included into many pediatric guidelines.

- The role of aprepitant in children has to be explored with further studies. The studies of neurokinin-1 receptor antagonists and also some newer 5-HT3 antagonists should be done in children receiving chemotherapy.

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