JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A review on antiemetic drugs used for chemotherapy induced nausea and vomiting in paediatric patients

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Abstract:

Chemotherapy induced nausea and vomiting (CINV) is a grieve symptom in children receiving cancer treatment that imparts their quality of life. More than 40 per cent of children receiving cancer treatment reported nausea and vomiting caused by chemotherapy even when antiemetic medications were used. With the recent approach in antiemetic drugs the current treatments of CINV have become highly effectual in reducing the adverse effects. In addition, there are emerging patient derived risk factors associated with CINV which should be decoded.

Objective- The aim of this review is to evaluate the current practice in antiemetic medicaments for paeditrics undergoing CINV.

Conclusion- The review highlighted a lack of conscientiously developed CINV pharmacological treatment for paeditrics patients. Contemporary studies have shown espousal of "triple therapy" regimen of antiemetic prophylaxis (5-HT3 antagonist, dexamethasone and neurokinin-1) as a foundation for prevention of CINV in paeditrics.

Key words- Nausea, Vomiting, Antiemetics, CINV, Chemotherapy, Paeditrics

Introduction:

In spite of remarkable development in antiemetic therapies, chemotherapy induced nausea and vomiting (CINV) is still a grieve symptom in children undergoing chemotherapy. [1][2] Nauseous clinical complications such as dehydration, electrolyte imbalance and physical strain can occur as a result of inadequate control on CINV. [3] Proper antiemetic treatment should be selected by evaluating the emetogenic risk of chemotherapy as a single agent and as a combination therapy. [4] The effect of CINV may become more intense and may impact the patient's aspect of life, leading to lack of patient consent and interfering with the ability to deliver more intensive chemotherapy regimens. [3][5][6] Here we focus on key principles that inform the background of CINV in paeditrics patients, reviewing the risk factors associated with CINV and aims to evaluate the current practice of antiemetic medication. Nearly all clinical studied for CINV are focused on adult population but we are considering paeditrics as our prime object.

Classification of CINV:

In terms of chemotherapy, vomiting can be classified according to five distinct CINV syndromes depending on onset and any prior patient response to antiemetic treatment:-

- Acute CINV- It appears within a few minutes of chemotherapy treatment onset and disappears within 24 h of its occurrence.

- Delayed CINV- It occurs 24 h following the start of chemotherapy and can be present in up to 80% of patients. It is usually most severe on the 3rd day and can last up to 7 days, and delayed nausea and emesis is more prevalent in patients with uncontrolled acute CINV.

- Anticipatory nausea and emesis-It may be present in patients before treatment begins, depending on emotional distress or perceptions of the patient. It is present in around 25 percent of paeditrics patients and tends to be a conditioned response to uncontrolled CINV that occurs during previous chemotherapy courses.

- Breakthrough CINV- It refers to the occurrence of nausea and emesis during previous courses of chemotherapy despite the administration of appropriate CINV prophylaxis.

- Refractory CINV- It is characterized as nausea and emesis that recur during subsequent course of chemotherapy and does not respond to antiemetic treatment or prophylactic changes. [7][8][9][10]

Risk Factors Linked with CINV:

Many efforts have been made to identify the anticipating risk factors for CINV in paeditrics. In addition to treatment-related factors such as dosage and intrinsic emetogenicity of chemotherapy drugs, a number of patient-related factors such as age, sex, anxiety and high expectations of nausea pre-treatment etc. have been seen. And in each patient, anticipatory nausea as mentioned above is distinctive based on their previous experience with CINV and plays a factor in the total risk of emetogenicity with each subsequent

encounter. [11] For paeditrics, only a few studies have been carried to investigate factors influencing the risk of CINV. Absolute protection rate against CINV was obtained with intravenous ondansetron administered alone for moderately emetogenic chemotherapy, or in combination with dexamethasone for a highly emetogenic regimen, varied among children and correlated with patient age, Children under 3 years of age had full CINV control rates that were substantially higher than older children and adolescents. There persists a gap between clinical and therapeutic practice, particularly in terms of treating children. None of the scoring systems include evidence-based suggestions for acute and delayed antiemetic treatment in children, thus CINV remains a distressing and partially controlled side effect.[12]

Main classes of antiemetic drugs:

The type of antiemetic drug used in the treatment of CINV has a huge impact on paeditrics, an in-depth knowledge of different antiemetic drugs is mandatory. The main classes of antiemetic drugs included in CINV prevention are:-

5-HT3 Antagonist-

5-HT3 (serotonin) has known to be the most effective drug in CINV treatment. Antagonists of 5-hydroxytryptamine3 (5-HT3) receptors (ondansetron, granisetron, tropisetron, palonosetron) are used in CINV control.[13] In children receiving highly or moderately emetogenic chemotherapy over several days Palonosetron is a second-generation 5-HT3 receptor antagonist that has been shown to achieve better control of emesis compared with ondansetron. [14] 5HT3 selective antagonists show their action on receptors present in both central nervous system targets such as the area postrema, and the peripheral nervous system such as vagal afferents in the intestine. They are a well tolerated class of drugs, with no limiting toxicity at typical doses. The most typical adverse side effects include headache and constipation. However, the oral and intravenous administrations are similar to therapies. 5-HT3 antagonists form the backbone of antiemetic prophylaxis regimens for moderate to highly emetogenic chemotherapy. A 5-HT3 antagonist combination with dexamethasone offered better antiemetic power than a 5-HT3 antagonist alone.Several randomized controlled trials and meta-analyses in children, have shown their efficacy.[15][16]

Neurokinin-1 Antagonist-

A brand new antiemetic drug “Aprepitant” (Neurokinin-1 Antagonist receptor) has been approved for treatment of emetogenic chemotherapy. Neurokinin is a constituent of group of protein called tachykinins that have multiple regulatory functions. In the central nervous system, including the postrema region, neurokininin-1 receptors are present diffusely and also have peripheral targets in the gastrointestinal system. Aprepitant seems to be well tolerated drug but, due to its hampering effect on cytochrome P450 isoenzyme 3A4, it can lead to significant drug interactions, resulting in the need for dose modification of concomitant therapy.[17][18][19]

Corticosteroids-

Corticosteroids, such as dexamethasone and methylpredinisolone, are commonly used to prevent acute and late CINV in paeditrics patients. Corticosteroids have a major advantage in supplying antiemetic regulation for all nausea, acute, and delayed emesis. They are often used as single-agent therapy for low emetogenic chemotherapy and in combination with 5-HT3 (±neurokinin-1 antagonists) for moderate to highly emetogenic chemotherapy but long-term use may lead to moderate to severe problems with insomnia, hyperglycaemia, epigastric discomfort, agitation, increased appetite, weight gain and acne. [20]

Triple Therapy Antiemetic Regimen:

5-HT3 antagonists, corticosteroids and neurokinin-1 antagonists are the main classes of drug with high therapeutic action in CINV prophylaxis as described above. Each one has different mechanism of action but their combination has shown to impart maximum antiemetic control. It has emerged out to be the most extensively recognized antiemetic prophylaxis and often referred to as “Triple Therapy” antiemetic regimen.[21]

Nonetheless, the "triple therapy" regimen was limited to children > /= 12 years of age undergoing highly emetogenic chemotherapy due to a lack of safety and efficacy evidence in paeditrics. The neurokinin-1 antagonists were the class of antiemetic drugs with the least amount of paeditrics data. Therefore, only a 5-HT3 antagonist and dexamethasone is prescribed as prophylaxis for children under 12 years of age, even for extremely emetogenic chemotherapy, a drug-typical regimen rated as moderately emetogenic. Since then, there has been a revolution of paeditrics-based data in the field of CINV prophylaxis. [22]

Complications:

Nausea and vomiting may be multi-factorial in paeditrics cancer patients. It will represent an evaluation of the symptoms. Structural, psychological, chemical, and metabolic or a mixture of causes can cause nausea and vomiting. Causes such as pain, anxiety, hepatosplenomegaly, bowel obstruction, metastasis or increased ICP should also be considered when assessing paeditrics cancer patients with suspected CINV. These include the following:

- Direct effects of tumor by stretching organs of the gastrointestinal system or causing obstruction.
- Postoperative obstruction (in patients who have had abdominal surgery)
- Increased intracranial pressure
- Opioid induced vomiting

Children are particularly vulnerable to electrolyte imbalances, weight loss and dehydration. Consequently poor nutrition may impact on their intolerance to additional chemotherapy. The actual vomiting experience causes physical and emotional trauma for the infant as well as for the parents. Such anxiety can have significant effects on the patient's normal activities and quality of life. Among the contributing factors are patient characteristics and chemotherapy agents; the latter potentially being the most significant risk factor. [23][24]

Discussion:

Nausea and emesis appear to be the most significant adverse side effects in children undergoing chemotherapy, following the introduction of new agents for the treatment of CINV. Existing recommendations for the prevention of CINV in children are distinguished by a lack of conclusive evidence, which results in insufficient regulation of symptoms in paeditrics patients receiving high emetogenic potential anti-neoplastic drugs. Therefore, in most paeditrics guidelines, newer antiemetic medications that are in clinical use for CINV management in adult cancer patients remain missing. Children are not small adults, and there may be very different metabolic and pharmacological studies with regard to effectiveness and side effect danger.[25] Some clinical studies have shown that the emetic behavior of each child develops according to a unique pattern due to various influencing factors such as sex, age, or earlier chemotherapy, and needs appropriate supervision and personalization during anti-neoplastic therapy. In addition, the fact that patients that experience acute and delayed CINV more often

than is considered by clinicians should be taken into account by physicians involved in prescribing chemotherapy, with the result that patients do not receive adequate prophylaxis and care for their nausea and vomit. It is necessary to use adequate antiemetic prophylaxis to ensure optimal care and to reduce the CINV complications.[26]

Conclusion:

A number of recent paeditrics studies have developed recommendations for children's CINV prophylaxis. The use of combination therapy with a backbone of 5-HT3 antagonists, dexamethasone and neurokinin-1 antagonists has been demonstrated to provide better antiemetic control for both acute and delayed phases. Despite the advances made by CINV prophylaxis over the past two decades, there are a number of areas that still lack any or at least any robust, paeditrics-specific information. There are still several anti-neoplastic medications with little paeditrics data on the risk of emetogenicity. Through faithfully adhering to evidence-based antiemetic guidelines, the occurrence of one of the most feared and troublesome adverse effects of anti-neoplastic therapy in children can be drastically reduced. The most recent changes in the area based on randomized controlled trials have enabled this optimal control to be expanded to patients > /=6 months old.

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