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Ondansetron in the control of chemotherapy-induced and radiotherapy-induced emesis in children with malignancies

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The management of chemotherapy-induced nausea and emesis presents a major problem in children with cancer. The anti-emetic properties of the 5-HT_3 receptor antagonist ondansetron are well documented in adults receiving cytotoxic chemotherapy. Experience in the treatment of children is still limited. Here we present a review of the literature on the anti-emetic treatment with ondansetron in children. Moreover, we provide recommendations on the use of ondansetron during anti-neoplastic chemotherapy and radiotherapy in pediatric oncology.

Key words: Chemotherapy- and radiotherapy-induced nausea and emesis, children, ondansetron, pediatric cancer patients.

Introduction

In recent years, significant advances have been made in the treatment of childhood malignancies with cytotoxic drugs and radiotherapy, but in these patients nausea and emesis remain a major problem of many chemotherapeutic regimens. For example, cisplatin has become established as one of the most active chemotherapeutic agents in a variety of malignant tumors, but its potential to cause emesis in all patients results in considerable distress and inconvenience to children, parents and medical staff.[1–5]

Excessive vomiting in children may result in electrolyte imbalance and dehydration, potentiating the nephrotoxicity of drugs and delaying the clearance of many substances after high-dose infusion treatment. However, in addition to acute emesis, children may continue to suffer from the emetic effects of their chemotherapy after discharge from hospital, especially after receiving chemotherapy associated with delayed emesis. Far too often, these symptoms become debilitating and patients become physically incapable of receiving further chemotherapy or are so psychologically distressed that they or their parents may refuse subsequent potentially curative chemotherapy and radiotherapy. Patients who suffer a distressing first course of chemotherapy are particularly prone to develop nausea and even vomiting in anticipation of subsequent courses. Anticipatory emesis is a difficult condition to treat and underlines the importance of achieving good control first time with an effective anti-emetic regimen.[1,2]

Over the past decade, advances in the understanding of the physiology and pharmacology of nausea and vomiting have led to a better ability to control these symptoms. The mechanisms of cytotoxic drug- and radiotherapy-induced emesis appear to involve a release of serotonin from one of the largest 5-HT pools in humans, the enterochromaffin cells in the gastrointestinal tract. This release is thought to be primarily important in the initiation and maintenance of the vomiting reflex. It is suggested that local high concentrations of serotonin activate the 5-HT_3 receptors located on vagal visceral afferent fibers. This information is relayed to the vomiting system. Thus the chemoreceptor trigger zone (CTZ) and the vomiting center, both located in the medullary lateral reticular formation, are stimulated via the vagus nerve. Clinical data obtained with ondansetron, a highly selective and potent 5-HT_3 receptor antagonist, showed that sustained blockade of 5-HT_3 receptors could lead to excellent control of cytotoxic drug- and radiotherapy-induced nausea and emesis.[3,6] None of the traditionally prescribed anti-emetics are entirely effective, either alone or in combination, and many are associated with unpleasant side effects, which may be more pronounced in children. In particular, high-dose metoclopramide, which is effective in the management of emesis following cisplatin treatment, is associated with severe extrapyramidal side effects in children. Other drugs such as phenothiazines, benzodiazepines and butyrophenones may

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also be effective. However, many children dislike the sedation and/or agitation associated with these agents. Here we review the current literature on ondansetron in the control of chemotherapy- and radiotherapy-induced emesis in children with malignancies.

Ondansetron metabolism and pharmacokinetics

The pharmacokinetics and metabolism of ondansetron have been extensively studied in both healthy volunteers and cancer patients.[7] Hepatic oxidative metabolism accounts for more than 95% of ondansetron clearance from the body. The major excreted metabolites are conjugates of 7-hydroxy- or 8-hydroxyondansetron, which appear to contribute little to the activity to the parent drug. Ondansetron plasma clearance averages approximately 0.45 l/h per kg body weight. Clearance decreases with increasing age, whereas the volume of distribution remains unchanged. The result is an increase in mean plasma half-life from 3.5 h in young volunteers (aged 18–40 years) to 5.5 h in volunteers over 75 years of age.[7] Clearance and volume of distribution are higher in young (aged 7–12 years) cancer patients, resulting in a mean plasma half-life of 2.5 h.[8]

Clinical studies with ondansetron in children

Ondansetron has been shown to be very effective in abolishing emesis caused by different single-drug and combined cytotoxic regimens in many trials in adults with cancer.[3,6] Pediatric studies with ondansetron have shown it to be well tolerated and effective with minimal side effects in children.[1,2,9,12]

In an open, uncontrolled study by Carden *et al.*[9] ondansetron was given to 20 children aged 4–18 years. All patients had previously received cytotoxic agents and were treated with a combination chemotherapy regimen that included cyclophosphamide (1000 mg/m^2 on day 1) and cytarabine (75 mg/m^2 on days 2 to 5). Ondansetron was administered as a single intravenous bolus at two different sequential doses. The first 10 patients received ondansetron 5 mg/m^2, and the other 10 patients received treatment with 3 mg/m^2. Progression to the second dosage was contingent upon the adequacy of the anti-emetic response achieved by the patient cohort at the first dose level. Both groups of patients also received ondansetron 2, 3, or 4 mg orally at a dose based on their body surface area (BSA). The first oral dose of ondansetron was given concurrently with the intravenous bolus. It was followed by 13 additional doses given every 8 h. Unfortunately, no statistical analysis to compare differences in response or adverse effects between the two groups was performed. However, the investigators concluded that ondansetron is remarkably effective as a single agent and is associated with minimal adverse effects.

Pinkerton *et al.*[10] studied the effects of ondansetron against acute and delayed nausea and vomiting in 30 pediatric patients (aged 2–16 years) with various solid tumors. Patients were stratified into one of four groups. Ondansetron was administered as a parenteral loading dose of 5 mg/m^2, followed by oral maintenance doses given every 8 h for 5 days. Maintenance doses were also based upon patients' BSA. Patients with BSA < 0.3, 0.3–0.6, 0.6–1.0, and > 1.0 m^2 received 1, 2, 3, and 4 mg of ondansetron, respectively. Children were observed in hospital for 1 day after administration of the cytotoxic drugs. Evaluation for the following days was accomplished on an outpatient basis by means of a questionnaire. It was found that 92%, 88%, 80% and 50% of patients who received carboplatin-, cyclophosphamide-, ifosfamide- and cisplatin-containing regimens, respectively, achieved a complete or major emetic response (two or fewer emetic episodes) during the first 24 h. Anti-emetic efficacy was maintained through day 5 in patients who received either carboplatin- or cyclophosphamide-containing therapies. In contrast, patients who were treated with either cisplatin- or ifosfamide-containing regimens developed significant late-onset nausea, vomiting, or retching (more than three emetic episodes) from 24 to 120 h after cytotoxic administration.

Similar results were reported by Jürgens and McQuade[1] and Hewitt *et al.*[2], both representatives of the European Paediatric Emesis Study Group. Jürgens and McQuade[1] report on 429 children (aged 6 months to 17 years) given ondansetron at a variety of emetogenic cancer treatments in three open, multicentre European studies. The dosage of ondansetron was identical to that used in the study by Pinkerton *et al.*[10] Sixty-eight per cent of all ondansetron treatment days (2131) were free of emesis. When analysed according to the most emetogenic agent given, 36%, 59% and 75% of children reported less than three emetic episodes on their 'worst day', respectively, during cisplatin, ifosfamide and other less emetogenic chemotherapy

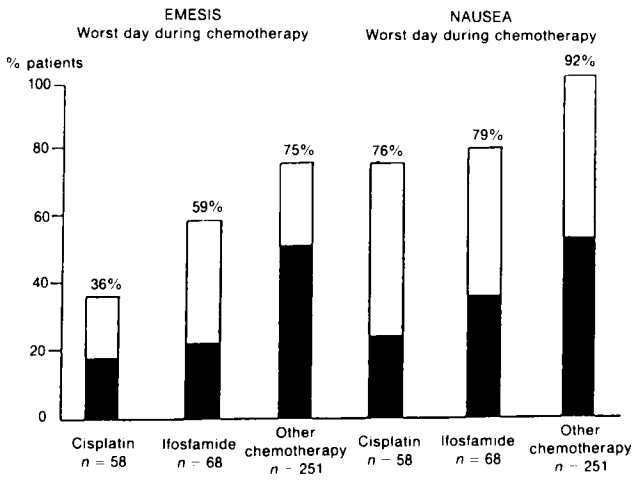

Figure 1. Efficacy: emetic episodes and nausea by chemotherapy regimen. Emetogenic chemotherapy was given for up to 8 days. □, major response/mild nausea; ■, complete response/no nausea. (Reproduced with permission from Jürgens and McQuade[1].)

(Figure 1). During conditioning for bone marrow transplantation with cyclophosphamide and total body irradiation, 80% and 57% of patients experienced less than three emetic episodes (Figure 2). The overall incidence of adverse events was low and headache (reported in 4% of patients) was the only event reported by more than 1% of patients.

Hewitt *et al.*[11] reported on the efficacy of ondansetron in 15 children (aged 2–17 years) under preparation for bone marrow transplantation using cyclophosphamide and total body irradiation. Of 100 evaluable patient days, 83 (83%) were without any vomiting and retching. There were no significant side effects noted, only transient

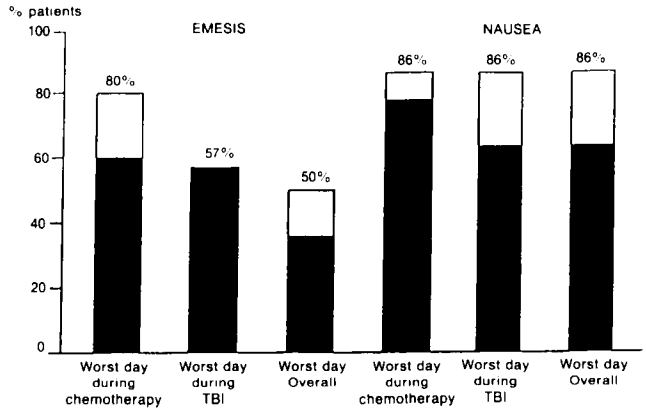

Figure 2. Efficacy: emetic episodes and nausea associated with chemotherapy and total body irradiation (TBI) preparation for bone marrow transplantation ($n = 15$). (Reproduced with permission from Jürgens and McQuade[1]). □, major response/mild nausea; ■, complete response/no nausea.

elevation of liver enzymes were noted on two patients.

In an open-label, noncomparative trial in the US, Bryson *et al.*[13] studied 21 pediatric cancer patients (aged 4–18 years) who received three intravenous doses of 0.15 mg/kg of ondansetron at 4 h intervals. In this study the anti-emetic efficacy, pharmacokinetics and safety of ondansetron were investigated. Pharmacokinetic results indicated that ondansetron half-life ($t_{1/2}$) in patients under 12 years of age is shorter (2.5 h) than in older pediatric patients and adults. Sixty-two per cent of the patients had no emetic episode during the study. In addition, the authors could show that no emetic episode was observed if the area under the infusion curve (AUC) was 300 ng/h per ml, regardless of the cytotoxic chemotherapy.

In an open, uncontrolled study performed by Sullivan *et al.*,[14] 15 young cancer patients (aged 3–11 years) received ondansetron according to the treatment recommendations by Pinkerton *et al.*[10] for different chemotherapy regimens. Although not all patients were naive to cytotoxic chemotherapy, sufficient anti-emetic control could be achieved.

Recently, Csaki *et al.*[12] presented an open, noncomparative study of 33 children with cancer (aged 1–18 years) treated with different cytotoxic regimens, including high-dose cisplatin (120 mg/m^2), intermediate-dose cisplatin (60 mg/m^2), or other highly emetic drugs. Ondansetron was administered in the same treatment schedule published by Pinkerton *et al.*[10] The analysis of group A (22 patients with osteosarcoma) receiving high-dose cisplatin (120 mg/m^2) revealed complete response (CR) or major response (MR) in 74.2% of the courses on the day of cisplatin administration. However, a 'worst day analysis' revealed no significant difference between courses given with ondansetron or with other agents (metoclopramide, dexamethasone, levopromazine) (CR + MR 51.6% *vs* 63.6%).

Stevens[4] demonstrated the anti-emetic properties of ondansetron on a twice-daily dosage regimen in children receiving non-cisplatin chemotherapy. In a randomized study, 61 patients received either ondansetron (5 mg/m^2 or 8 mg/m^2) intravenously or orally (2, 4 or 8 mg) or a 'customary' anti-emetic treatment (metoclopramide, dexamethasone, nabilone, domperidone, haloperidol, chlorpromazine). Sixty per cent of patients (18 out of 30) receiving ondansetron reported less than three emetic episodes on their 'worst day', compared with 47% (14 out of 30) on 'customary' treatments. Similarly, 73% (22 out of 30) and 57% (17 out of 30) of patients

reported no nausea or mild nausea after ondansetron and 'customary' treatment, respectively.

Unfortunately, so far there are no data available of controlled, randomized, double-blind trials exploring fully the encouraging anti-emetic potential of ondansetron in children with cancer.

Tolerability

In the biggest studies performed in children so far, ondansetron was well tolerated and the overall incidence of adverse events was low (Jürgens and McQuade,[1] 14%, Hewitt *et al.*,[2] 13%). Headache was the commonest single side effect (3.3–4%). Unexpected changes in laboratory data in a few patients were limited to alterations in liver function tests and included increase in bilirubin, increase in aspartate transferase, increase in alanine transferase and increase in γ-glutaryl transferase,[2] but the changes in laboratory parameters were assessed by the investigators as possibly related to ondansetron. No extrapyramidal side effects were reported.

One serious adverse event, renal failure (considered to be possibly not related to ondansetron) in a 13-year-old girl with osteosarcoma who had received high-dose methotrexate (13g/m^2), was reported.[1]

Dosage and administration in children

A loading dose of ondansetron 5 mg/m^2 infused over 15 min prior to the first chemotherapy should be administered in children with BSA < 1.2 m^2 (BSA > 1.2 m^2, 8 mg). Subsequent doses should be given every 8 h until the last dose of chemotherapy. Thereafter ondansetron should be administered orally, with the first dose given within 2 h of the last intravenous dose. The oral preparation should be given 8-hourly at doses calculated from the BSA (BSA < 0.6 m^2 given 2 mg; BSA 0.6–1.2 m^2 given 4 mg; BSA > 1.2 m^2 given 8 mg) and should be continued for 5–7 days if the patient has received a regimen containing cisplatin or 3 days for other non-cisplatin regimens.

Conclusions and future perspectives

Ondansetron is effective in children receiving a wide variety of cytotoxic regimens. Severe nausea and emesis that cannot be adequately controlled by conventional anti-emetics generally show a good response to ondansetron. Adverse events are relatively uncommon and usually mild. Although only a few open-label, noncomparative trials have been performed in children, most pediatric oncologists all over the world have included ondansetron in their treatment repertoire. However, many questions have still not been answered. Prospective, randomized studies are therefore a necessary task to evaluate the efficacy of ondansetron in children and to optimize the prophylactic anti-emetic treatment in pediatric cancer patients.

As studies in adults have shown enhanced efficacy when dexamethasone is added to ondansetron, double-blind randomized trials should be undertaken in children who receive high-dose cisplatin to compare the efficacies of ondansetron and ondansetron plus dexamethasone.[15] Moreover, based on clinical data obtained in adults, further studies may also be needed to evaluate the efficacy of different dose schedules.[5,16,17] In addition, combinations of conventional anti-emetic drugs (dexamethasone, metoclopramide, lorazepam, scopolamine patch) with ondansetron should be investigated in an attempt to gain complete control of chemotherapy-induced emesis in children.[18]

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