Ondansetron oral disintegrating tablets for the prevention of postoperative vomiting in children undergoing strabismus surgery

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Abstract: Strabismus surgery in pediatric patients is associated with a high incidence of postoperative nausea and vomiting (PONV). Ondansetron disintegrating tablets (ODT), an oral freeze-dried formulation of the 5-HT_3 antagonist, are well-tolerated and have been shown to reduce chemotherapy-induced vomiting. The purpose of this study was to assess the efficacy of the ODT in preventing postoperative vomiting (POV) in children undergoing strabismus repair. Healthy children aged 4–12 years of age were administered a 4 mg ODT 30 minutes prior to the induction of general anesthesia. Induction and maintenance of anesthesia were standardized; each child received acetaminophen and ketorolac pre-emptively for analgesia. This study group was compared with a historical control group who received a placebo in previously conducted identical trials of POV. The 35 children included in this study were compared with 31 controls. The incidence and severity of POV and use of rescue antiemetics were significantly lower in children who received ODT compared with placebo ($p \leq 0.001$). The acute complete response (ie, no emesis and no rescue antiemetics in 24 hours) was 76% in the ODT group compared with 16% in the controls ($p \leq 0.001$). Results suggest that ODT given preoperatively reduces the incidence and severity of POV in children undergoing strabismus surgery.

Keywords: pediatrics, postoperative, vomiting, ondansetron

Introduction

The incidence of postoperative nausea and vomiting (PONV) in children varies from 5% to 80% (Baines 1996). The etiology is complex and multifaceted, including patient-related factors, type of surgical procedure, choice of anesthetic agents, and postoperative management (Sung 1996). Children undergoing strabismus surgery are particularly prone to PONV. Postoperative vomiting (emesis) is the forceful expulsion of gastrointestinal contents through the mouth (Kovac 2000) and is mediated by a variety of neurotransmitters including serotonin which binds to serotonergic (5-HT_3) receptors located both peripherally on the vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema (Borison 1989). The serotonin receptor antagonists (including ondansetron, dolasetron, granisetron, and tropisetron), purportedly block the effects of serotonin in the chemoreceptor trigger zone, nucleus tractus solitarius, and vagal afferents (Wadibia 1999). These antiemetic agents have been shown to reduce chemotherapy induced nausea and vomiting, as well as PONV. Intravenous (IV) ondansetron administered in doses ranging from 40–200 mcg/kg has been extensively studied for prevention of PONV in children undergoing strabismus surgery (Bowhay et al 2001).

An innovative freeze-dried ondansetron oral disintegrating tablet (ODT) was developed to allow for disintegration on the tongue with dissolution and rapid absorption in the gastrointestinal tract in the absence of water (see http://us.gsk.com/). The active ingredient in ODT is the racemic form of ondansetron, and a 4-mg ODT contains 4 mg of ondansetron base. Davidson and colleagues (1999) have demonstrated

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equivalency of ODT 8 mg to oral ondansetron 8 mg in highly emetogencic chemotherapy. The pharmacokinetic data suggests that ondansetron is readily and completely absorbed from the gastrointestinal tract following oral administration (Roila and Del Favero 1995). In children undergoing highly emetogenic chemotherapy, ODT (4–8 mg) showed similar efficacy for complete control of emesis compared with IV ondansetron; 93% versus 92% respectively, and was considered safe, well tolerated and cost effective (Corapcioglu and Sarper 2005). In children undergoing adenotonsillectomy, a fixed dose of 4 mg ODT resulted in the number needed to treat (NNT) = 2.86 with a relative risk reduction for PONV of 50%. Additionally, the ODT was found to be acceptable in taste with 87% of patients willing to take the medication in the future (Cohen et al 2005). The properties of ODT make it a potentially useful agent in children who cannot swallow water or pills during the perioperative period. The purpose of this study, therefore, was to determine the efficacy of ODT in reducing the incidence and severity of POV in children undergoing outpatient strabismus surgery.

Methods

Approval from the University of Michigan Institutional Review Board (IRB) and written informed consent from a parent or legal guardian was obtained for this prospective, observational, historically controlled study. Healthy children aged 4–12 years of age, ASA I-II, scheduled to undergo strabismus surgery were recruited. Those with a history of cardiac, hepatic, renal or neurological impairment, prior severe PONV, known sensitivity to 5-HT_3 receptor antagonists, and requirement for premedication were excluded.

Preoperatively, each child received an oral dose of acetaminophen (15 mg·kg^{-1}) followed by a 4 mg ODT 30 minutes prior to induction of anesthesia. Acceptability of the ODT was scored using a 4 point scale (1 = readily, 2 = reluctant, 3 = held down, 4 = refused). General anesthesia was induced with sevoflurane via facemask. A laryngeal mask airway (LMA) was placed and anesthesia was maintained with isoflurane. Ketorolac (0.5 mg·kg^{-1}) was administered following placement of the IV intraoperatively. At the completion of the surgery, the stomach was aspirated via an oral-gastric tube and the LMA was removed at the discretion of the anesthesiologist. Strict adherence to the protocol were maintained by research personnel who were present the entire time of the surgical procedure.

Postoperatively, children were observed for any episode of POV or retching. Two or more episodes of vomiting or retching were treated with metoclopramide 0.15 mg·kg^{-1} IV as a rescue medication. Pain was assessed using the Faces, Legs, Activity, Cry and Consolability (FLACC) observational pain scale and children with scores ≥4 were treated with morphine sulfate 0.05 mg·kg^{-1} IV titrated per routine practice. Parents were telephoned the day after surgery to assess further POV, treatment and potential adverse effects. Additionally, parents rated their satisfaction with the prevention and treatment of POV as 1 = very dissatisfied, 2 = dissatisfied, 3 = satisfied, 4 = very satisfied.

Historical placebo controls from previous studies of POV conducted at the same institution using the same identical anesthetic technique and research protocol were used for statistical comparison (Munro et al 1999; Wagner et al 2003). These studies were placebo controlled studies of POV in children undergoing strabismus surgery. Patients were randomized to IV dolasetron in a fixed dose and weight based dose versus IV sodium chloride or oral granisetron compounded in strawberry syrup versus strawberry syrup alone each in equivalent volumes. For the purposes of analyses, the severity of POV was classified as mild (1 episode), moderate (2 episodes), or severe (3 or more episodes). Additionally, the primary efficacy measure was an acute complete response (ACR) which was defined as no emetic episodes or rescue antiemetic medication use within 24 hours of ODT 4 mg administration. Categorical data such as ACR, and the incidence and severity of PONV were compared using chi-square with Fisher's exact tests as appropriate. Patient age, weight, and other parametric data were compared using unpaired t-tests. Data are reported as mean + SD or n (%) with p values of <0.05 considered statistically significant.

Results

A total of 49 children were enrolled in the study. Fourteen children were excluded due to protocol violations such as administration of morphine intraoperatively or use of additional prophylactic antiemetics. Data from 35 children who received ODT are, therefore, reported. The historical control group included 31 children who received placebo in 2 studies as described previously (Munro et al 1999; Wagner et al 2003). The demographics and perioperative data were similar between the placebo and ODT groups, with the exception that children in the ODT group had a significantly longer anesthetic duration compared with controls (Table 1).

Outcome data including the incidence and severity of POV, use of rescue medications, and ACR are presented in Table 2. One hundred percent of the patients readily accepted the ODT and no children were admitted to the hospital as a

Table 1 Demographics and perioperative data of the study groups

	ODT (n = 35)	Placebo* (n = 31)
Age (yrs)	6.1 ± 1.7	6.7 ± 2.4
Weight (kg)	24.6 ± 6.9	24.9 ± 8
Gender male (%)	51	58
ASA/I/II (%)	80/20	70/30
Duration of anesthesia (min)	77 ± 19	60 ± 17**
Received morphine (PACU)	22 (63%)	15 (48%)
Postoperative length of stay (min)	116 ± 67	127 ± 36

Notes: *Placebo controls compiled from historical data in previous studies of PONV; **p < 0.05 compared with ODT

result of POV. Nausea was only assessed in children able to verbalize and understand the concept of nausea by a yes/no response. The incidence headache, abdominal pain, emergence agitation and other side effects were similar between groups. The respective incidences for the ODT compared with placebo were 72.7% versus 67.7% for headache, 96.9% versus 93.5% for abdominal pain, and 2.9% versus 0.0% for emergence delirium

Discussion

Postoperative nausea and vomiting remain a leading cause of morbidity in pediatric surgical patients, contributing to bleeding, dehydration, wound dehiscence and the potential for pulmonary aspiration (Rose and Watcha 1999). Additionally, severe PONV occurs with a frequency of 1%–3% and may result in unanticipated hospital admission leading to increased institutional costs. A recent multi-center study involving 1257 children aged birth-14 yrs old showed that strabismus surgery was an independent risk factor for postoperative vomiting. Of all risk factors it was the most significant with an OR of 5.2 similar to other reported incidences of up to 87%. Findings from this study demonstrate that prophylactic administration of ODT in a fixed dose of 4 mg reduced the incidence and severity of PONV in young children undergoing strabismus surgery (Eberhart et al 2004). Additionally, recent studies suggest that ODT is similarly useful for the prevention of PONV in children. Cohen and colleagues (2005) compared 4 mg ODT versus placebo in children undergoing adenotonsillectomy. Although patients also received intraoperative dexamethasone, the ODT group experienced significantly less vomiting and the ODT was readily accepted (Cohen et al 2005). In adult patients Gan and colleagues (2002) evaluated the ODT in patients undergoing outpatient gynecological laparoscopy with general anesthesia. Patients received 4 mg of IV ondansetron at induction and either 8 mg ODT or placebo prior to discharge. The ODT group experienced less severe nausea and fewer episodes of vomiting after discharge from PACU compared with the placebo group (Gan et al 2002). A study in craniotomy surgery patients also evaluated the postoperative administration of the ODT in an 8 mg dose compared with placebo as rescue therapy for PONV. Patients who received the ODT required less rescue therapy with metoclopramide than did the placebo group (Hartsell et al 2005). It appears that the ODT formulation may be efficacious for both the prevention and treatment of PONV in adults and possibly children.

Table 2 Postoperative outcomes in the study groups [n(%)]

	ODT (n = 35)	Placebo (n = 31)
POV in hospital	5 (14%)	21 (68%)**
POV in 24 hours	8 (24%)*	26 (84%)**
Rescue antiemetic in hospital	4 (11%)	17 (55%)**
Severe vomiting (≥3 episodes) /24 hrs	6 (18%)*	19 (61%)**
ACR	25 (76%)	5 (16%)**

Notes: *2 children lost to follow-up; **P ≤ 0.001 compared with ODT; ACR, Acute complete response, defined as no emetic episodes and no rescue medications within 24 hours.

The antiemetic efficacy of ODT has also been demonstrated previously for both radio-therapy, and chemotherapy induced nausea and vomiting (Davidson et al 1999; LeBourgeois et al 1999). A study in patients receiving cyclophosphamide chemotherapy compared 8 mg of oral ondansetron (OT) to 8 mg of ODT given twice daily for 3 days. The ODT was found to be equivalent to the OT for control of emesis with 89% of patients finding the taste acceptable (Davidson et al 1999).

Although there remains an ongoing debate over the appropriate timing of administration of the 5-HT_3 antagonists, a recent study by Madan and colleagues (2000) found no difference in efficacy between groups of children who received 0.1 mg/kg ondansetron IV at induction versus the end of strabismus surgery. It appears that in pediatric strabismus surgery, the time of administration of ondansetron is not related to efficacy (Madan et al 2000). Data suggest that ondansetron is completely and readily absorbed from the gastrointestinal tract following oral administration (Roila and Del Favero 1995). The time to reach peak concentration is between 0.5 to 2 hours with an approximate 160 liter volume of distribution and 70 to 76% plasma protein binding. The elimination half-life averages approximately 3.8 ± 1 hour and is extensively metabolized primarily through hydroxylation with subsequent glucuronide or sulfate conjugation.

Many factors contribute to POV that were not controlled for such as the use of reversal agents, hydration status, etc. Ideally, alternative methods of anesthesia and analgesia could

potentially lower the emetogenic potential in this population or the addition of other antiemetics such as dexamethasone in combination with the ODT. Ondansetron and dolasetron demonstrated comparative efficacy when used in combination with dexamethasone for POV prophylaxis in children undergoing tonsillectomy surgery (Sukhani et al 2002). Studies have also shown that the combination of metoclopramide with ondansetron was no more effective than ondansetron alone in children undergoing strabismus surgery. Hence the addition of metoclopramide in a prophylaxis regimen for PONV is probably not warranted (Kathirvel et al 1999). The ODT offers a unique, cost effective, formulation of a 5HT3 agent that is readily acceptable and safe in the pediatric surgical population. Additionally, while PONV is unpleasant for the child, it can also be disturbing to the parents and actually increase their time spent nursing the child in PACU.

Limitations

One important limitation of this study is the use of historical controls. It was felt that the use of a placebo control – in the case of children undergoing a known highly emetogenic surgery – was unethical given the known risks. Additionally data obtained from previous studies within the same institution provided a fairly equal distribution of matched controls that could be used for comparison. Although faculty and staff performing the surgeries had changed, the use of research personnel to ensure compliance with the identical protocols was critical.

Conclusion

The ODT is a readily acceptable form of a $5HT_3$ antagonist that can be safely used in children undergoing strabismus surgery for the prevention of POV. Additional studies are warranted to evaluate its utility in other types of pediatric surgeries with high incidences of POV and also its effectiveness as a rescue agent in the PACU.

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