Journal of Pediatric Surgery (2005) **40**, 1737–1740

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Journal of Pediatric Surgery

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Effectiveness of alimemazine in controlling retching after Nissen fundoplication

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Index words:
Retching;
Nissen fundoplication;
Alimemazine (trimeprazine, Vallergan)

Abstract

Background: Retching, an early component of the emetic reflex, is a common and distressing symptom in children after Nissen fundoplication. Alimemazine (trimeprazine, Vallergan; Castlemead, Herts, UK) is a phenothiazine derivative histamine$_1$ antagonist, which anecdotally relieves the retching symptoms.

Material and Methods: A prospective, double-blind, randomized, crossover, placebo-controlled study of 15 neurologically impaired children with retching after Nissen fundoplication over a period of 1 year (December 2002–December 2003). Patients were randomly allocated to receive 1 week each of alimemazine and placebo with crossover. A diary was maintained of retching episodes 1 week before, during, and 1 week after the trial. Dosage of alimemazine used was 0.25 mg/kg 3 times a day (maximum, 2.5 mg per dose). Statistical analysis was done using a paired Student's t test, where P value of less than .05 was considered significant. Results are presented as mean $\pm$ SD.

Results: Twelve parents completed the diaries (9 open, 3 laparoscopic Nissen fundoplication). Median age of the child was 36 months (8-180 months), median duration of retching was 4.5 months (1-52 months), and mean number of retching episodes per week was 60 $\pm$ 29.40. Mean number of retching episodes with alimemazine was 10.42 $\pm$ 9.48 vs 47.67 $\pm$ 27.79 with a placebo ($P < .0001$). No adverse effects were reported in those cases that completed the study.

Conclusion: At low dose, alimemazine (Vallergan) is a safe and effective drug in the management of retching after Nissen fundoplication.

Nissen fundoplication is the gold standard surgical treatment of intractable gastroesophageal reflux in children. Although effective in the management of gastroesophageal reflux, side effects from the procedure can develop postoperatively. These include retching, dumping, watery diarrhea, growth retardation, and small bowel obstruction [1,2].

Recurrent vomiting after Nissen fundoplication has been attributed to 2 different mechanisms because of recurrence of the gastroesophageal reflux or activation of the emetic reflex [3]. It is important to differentiate between the 2 because they have different underlying mechanisms and require different methods of treatment. Retching after Nissen fundoplication is a common and distressing symptom [3-8] and is not secondary to gastroesophageal reflux but is a feature of the emetic reflex.

The commonly used antiemetics such as dopamine receptor$_2$ antagonist (domperidone) and 5-hydroxytryptamine receptor$_3$ antagonist (ondansetron) are mostly ineffective at controlling retching in these patients. We report the

This paper was presented as a poster at the 51st Annual International Congress of British Association of Paediatric Surgeons, July 2004, at Oxford, UK.

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doi:10.1016/j.jpedsurg.2005.07.054

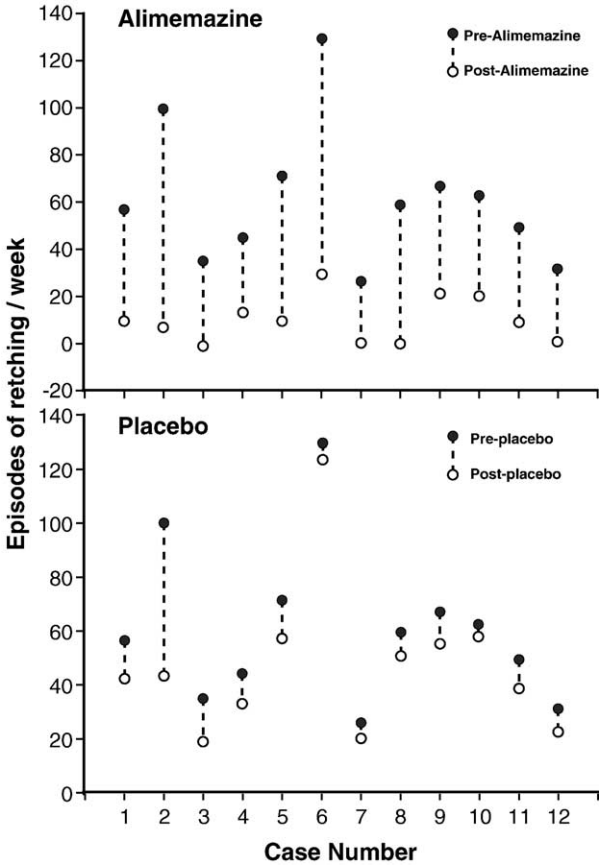

Fig. 1 Graphs showing the effect of alimemazine and placebo on episodes of retching in all patients.

results of the use of alimemazine (trimeprazine, Vallergan; Castlemead), a phenothiazine derivative histamine$_1$ (H_1) receptor antagonist, which anecdotally relieves the retching symptoms after Nissen fundoplication in children.

1. Material and methods

This prospective, double-blind, randomized, placebo-controlled crossover study was undertaken to assess the efficacy and safety of alimemazine, a phenothiazine derivative H_1 antagonist in controlling retching after Nissen fundoplication. All patients who developed retching after Nissen fundoplication and consented to the study were included irrespective of their preoperative retching state. Exclusion criteria were history of hepatic and renal dysfunction, and hypothyroidism. The study was approved by the Ethics Committee of the Great Ormond Street Hospital for Children, and informed consent was obtained. The medications were dispensed free of charge by the hospital pharmaceutical department as part of the National Health Service.

The patients were randomized to receive a week of alimemazine at a dose of 0.25 mg/kg 3 times a day (maximum, 2.5 mg per dose) and a week of placebo with a crossover. The parents were asked to maintain a diary of retching episodes and any side effects noticed a week before, during, and after the commencement of the drug/placebo. Seven cases had been on domperidone, which were discontinued before the commencement of the study. The outcome measures were frequency of retching. Statistical analysis was done using a paired Student's t test where P value of less than .05 was considered significant. Data are presented as mean ± SD.

2. Results

A total of 15 patients were enrolled in the study over a 1 year period (December 2002–December 2003), but completed diaries were received from 12 parents. The median age of these children (7 male, 5 female) was 36 months (8-180 months). One diary was lost in the post, 1 patient discontinued because of a viral illness and mild drowsiness, and 1 patient, because of social reasons. All patients were neurologically impaired and had undergone a Nissen fundoplication (9 open, 3 laparoscopic) for gastroesophageal reflux at a median age of 22 months (7-150 months). Nine children had experienced retching preoperatively, and all cases developed retching postoperatively with a mean of 60 ± 29.40 episodes per week. All patients were gastrostomy fed, and the medications were administered by gastrostomy. None of these patients had any diagnostic test for recurrent gastroesophageal reflux before institution of the drug. The trial was divided into 2 periods: alimemazine period and placebo period. The mean frequency of retching in the alimemazine period was 10.42 ± 9.48 vs 47.67 ± 27.79/wk in the placebo period (P < .0001) (Figs. 1 and 2). The mean frequency of

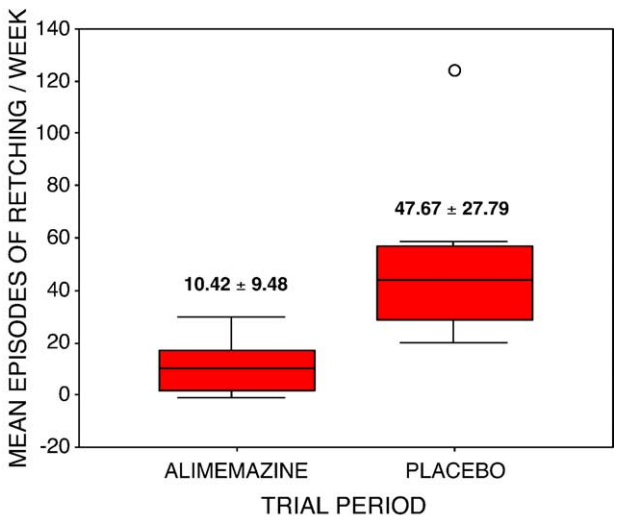

Fig. 2 Box plot comparing the mean episodes of retching during the drug and placebo trial period.

retching in the last week after the administration of drug/placebo was 51.20 ± 31.16/wk. No serious adverse effects and drowsiness were observed in those cases that completed the trial either with the drug or placebo.

3. Discussion

Gastroesophageal reflux is primarily because of a motility disturbance affecting the esophagus and the lower esophageal sphincter mechanism, leading to effortless regurgitation of gastric contents by a process related to the belch reflex. An association between gastroesophageal reflux and cerebral palsy was first reported in 1970 [9]. Since then, gastroesophageal reflux has been reported in a wide variety of neurologically impaired children. The pathogenesis of the reflux in these neurologically impaired children is likely to be because of foregut dysmotility secondary to central neurologic dysfunction [10]. Neurologically impaired children are less likely to respond to medical therapy and more frequently undergo antireflux surgery [11,12].

Retching is defined as the attempt to vomit without bringing back gastric contents. It may be described by such terms as *gagging*, *dry heaves*, and *attempting to vomit without results* [13]. It is the first part of the ejection phase of the emetic reflex and commonly occurs as a postoperative symptom [4-6] or, less commonly, as a preoperative symptom [3,8,14]. Persistent retching after antireflux surgery is a major concern for the patient, the parents, and the surgeon and occurs in 20% to 40% of cases [3,4,7,14-16]. It is more common in neurologically impaired children. Those children who retch preoperatively are more likely to do so postoperatively, but 25% of neurologically impaired children develop symptoms of retching postoperatively for the first time [3,17]. It has been postulated that, in neurologically impaired children, inhibition of the emetic reflex is lost or that it becomes hypersensitive and is activated in the course of normal everyday activity [17]. Fundoplication, by controlling gastroesophageal reflux, may disclose activation of the emetic reflex that was previously unappreciated, or the retching may result from sensitization of gastric vagal afferents, known to be a potent activator of the emetic reflex [18].

Retching, apart from being a distressing symptom after Nissen fundoplication, could contribute toward major postoperative complications such as disruption of the crural wrap with herniation of the wrap into the posterior mediastinum or disruption of the wrap itself, resulting in subsequent recurrent vomiting and failure of antireflux surgery [8,17,19,20].

Various methods used to control postoperative retching include the use of antiemetics (dopamine receptor$_2$ antagonists, 5-hydroxytryptamine receptor$_3$ antagonists), modulation of gastric vagal afferents (5-hydroxytryptamine receptor$_3$ antagonists, tricyclic antidepressants, small frequent boluses, or continuous gastric feeds), or bypassing the stomach altogether with jejunostomy feeds [17]. Most of the commonly used medications are ineffective in controlling retching symptoms as seen in our cohort where none of the children responded to antiemetics such as domperidone. Alimemazine is a phenothiazine H_1 receptor antagonist commonly used for its antipruritic and in high dosage for sedative effects. It is known to have antiemetic properties and a spasmolytic effect on the smooth muscle fibers [21]. It is effective in reducing the incidence of postoperative vomiting when administered as a premedication [22] and has been shown to be a good medication in the management of habitual vomiting in infants [21]. The use of alimemazine in these children resulted in a significant relief or abolition of retching symptoms without any side effects. However, in 1 case that discontinued the study because of a viral illness, mild drowsiness was reported. This could have been as a result of the viral illness, medication, or both the medication and the viral illness. It is not known whether alimemazine has any effect on gastric emptying because this was not measured in our study. The outcome was assessed based on clinical improvement of retching.

Alimemazine, at a low dose, is a safe and effective medication in controlling retching after Nissen fundoplication, which is very distressing for the child and the parents, and problematic for the surgeon. In addition, alimemazine may reduce the incidence of major postoperative complications of wrap herniation or disruption, leading to a failure of antireflux surgery. In our study, none of the cases were developmentally normal, and we were not selective in using the medication only in high-risk patients. However, a larger study needs to be undertaken to evaluate its use in different categories of patients over a longer period, with varying dosage regimens. It is recommended that the continued need for the drug is reviewed at regular intervals.

Acknowledgment

The authors thank Edward Kiely, Agostino Pierro, David Drake, and Joe Curry (Consultant Pediatric Surgeons, Great Ormond Street Hospital) for their valuable suggestions and help in recruitment of some of the patients.

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