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# **Is Rabeprazole A Safe Treatment for Gastroesophageal Reflux Disease in Children Ages 1-16 years?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies

Philadelphia College of Osteopathic Medicine

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## **Abstract**

Objective: The objective of the selective EBM review is to determine whether or not Rabeprazole is a safe treatment for GERD in children less than sixteen years old.

Study Design: Review of three randomized controlled studies. All three studies were published in English between 2007-2013.

Data Sources: Three randomized, un-blinded, controlled studies found using Medline and PubMed

Outcomes Measured: Each trial measured the adverse events that occurred with the use of Rabeprazole for the treatment of GERD in children less than sixteen years of age. This was done by using subjective reporting of treatment-emergent adverse events (TEAE's). Differences in the frequency of Treatment Emergent Signs and Symptoms (TESS) between the two treatment groups analyzed using the Fischer exact test and/or an appropriate nonparametric procedure.

Results: Three un-blinded RCT's were included in this review and it was found that Rabeprazole did not lead to any significant life-threatening treatment-emergent adverse events (TEAE's) in patients less than sixteen years of age. The most common adverse events were headache, nausea, cough, vomiting, abdominal pain, and diarrhea.

Conclusions: Based on these three trials, Rabeprazole is a safe treatment for GERD in children less than sixteen years of age. Each study showed a significant improvement of symptoms without any serious side effects when using Rabeprazole

Key Words: Rabeprazole, GERD, and children

## INTRODUCTION

Gastroesophageal Reflux “GER” is the passage of gastric contents into the esophagus with or without regurgitation or vomiting.<sup>1</sup> Physiologic “GER” is a very common and normal process in infants and slightly older children, however when this process becomes chronic and GERD develops it can lead to more serious symptoms such as swallowing difficulties that lead to weight loss, failure to thrive, and respiratory problems.<sup>1</sup> If these symptoms are not treated in time it can lead to long-term complications and a decreased quality of life for these children.<sup>1</sup> This paper evaluates three randomized controlled trials comparing the safety of Rabeprazole for the treatment of children less than sixteen years old with GERD.

Reflux is an extremely common complaint from patients with about 18-27% of North America’s population being effected.<sup>6</sup> So, because of its prevalence in this country it is relevant to the Physician Assistant profession. “GER” occurs in almost 100% of infants and is a normal process that typically resolves by the age of one.<sup>1</sup> Although, it is thought that approximately 2-22% of children between the ages of 3-18 years have GERD symptoms, but the exact statistics remain unknown.<sup>1</sup> The annual medical cost per patient in 2006 was \$6,878.<sup>6</sup> Medical services which include doctor visits, hospitalizations, ER costs, and lab costs totaled to about \$4,200, and prescription drug costs were estimated to be about \$922.<sup>6</sup> Gastrointestinal visits to the hospital, with GERD being the most common, represent about 8.9 million hospital visits each year.<sup>4</sup> Outpatient endoscopy’s used to diagnose GERD cost about \$32.4 billion dollars each year.<sup>4</sup>

The exact cause of GERD is unknown however there are many contributing factors that exacerbate symptoms. These factors include smoking, alcohol, obesity, eating large meals,

eating too soon or right before bed, hiatal hernias, pregnancy and diabetes.<sup>5</sup> Certain foods can increase GERD symptoms as well, these include chocolate, fried or fatty foods, caffeine, acidic foods such as fruits and tomatoes, and spicy foods.<sup>5</sup>

Typically the first line treatment for GERD involves lifestyle modifications.<sup>5</sup> These modifications include changes such as no food within three hours of bed, no large meals, raising the head of the bed, weight loss, avoiding alcohol, smoking cessation.<sup>5</sup> Also it is recommended that patients avoid the foods previously mentioned as they are known to increase GERD symptoms.<sup>5</sup> If these lifestyle modifications do not provide adequate relief for the patient the next step is the use of antacids, H2 blockers, or Proton Pump Inhibitors.<sup>5</sup> There are surgical options for treatment such as fundoplication, although these are usually reserved as a last resort.<sup>5</sup>

While there is currently no cure for GERD, all of the lifestyle modifications and medical treatment options listed above have seemed to improve symptoms in adult patients with GERD. This topic is being proposed to address the safety of this treatment option in younger populations to hopefully reduce symptoms and improve their quality of life.

## **OBJECTIVE**

The objective of this systematic review is to determine whether or not Rabeprazole is a safe treatment for GERD in children less than sixteen years of age.

## **METHODS**

Three un-blinded randomized controlled trials were used in this study. The population includes patients ages 1-16 years of age with a diagnosis of GERD. The intervention was the proton pump inhibitor Rabeprazole. All three of the studies were divided into two parts and the two parts were compared for TEAE's. Throughout the first section of the Haddad and Zannikos studies the patients were given approximately 0.14 mg/kg of Rabeprazole which is comparable to the lowest effective adult dose of the medication which is 10 mg, and they were observed for adverse events or reactions to the medications.<sup>1,3</sup> Then during the second part of the Haddad and Zannikos studies patients were randomized into two different groups and given a dose of Rabeprazole from the 0.5-1.0 mg/kg range.<sup>1,3</sup> In the first part of the James study the patients received the lowest effective 10 mg dose of Rabeprazole and observed for adverse events or reactions to the medication.<sup>2</sup> Then during the second part of the James study the patients were randomized into two different groups and they either received another 10 mg dose or a higher 20 mg dose of Rabeprazole and observed for adverse events or reactions to the medications.<sup>2</sup>

Key words used to research these articles were Rabeprazole, GERD, and children. All three articles were researched by the author and obtained through either Medline or PubMed. The articles were published in English and published in peer-reviewed journals. These articles were chosen based on the types of studies and relevance to the clinical question. The inclusion criteria for this search included randomized controlled trials in which the outcomes directly benefited the patient population in the selected age range. Exclusion criteria included patients

over the age of sixteen, pregnant or lactating patients, patients with allergies to PPI's, H. pylori infection, or previous acid lowering surgery or previous esophageal/gastric surgery. The statistics used and reported were numbers needed to treat (NNT), relative risk reduction (RRR), absolute risk reduction (ARR), and p-values. Table 1 displays the characteristics and demographics included in these studies.

**Table 1 – Demographics and Characteristic of included studies**

Study	Type	# Pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W/D	Interventions
Haddad <sup>1</sup> (2013)	RCT	127	1-11	Pts ages 1-11 who have endoscopically proven GERD	-Allergies to PPI's -H. Pylori infection	19	Rabeprazole 10 mg and 20 mg once daily orally
James <sup>2</sup> (2007)	RCT	19	12-16	Pts ages 12-16 with a clinical dx of GERD and minimum body weight of 30 kg	-evidence of other significant health condition -pregnant/lactating females -unwilling to refrain from smoking/drinking alcohol -drug allergy/sensitivity to PPI's -significant viral/bacterial infection within 1 month of screening -definitive acid lowering surgery or previous esophageal/gastric surgery	1	Rabeprazole 10 mg and 20 mg once daily orally
Zannikos <sup>3</sup> (2011)	RCT	24	1-11	Pts ages 1-11 with GERD and a minimum	-history of or current clinically significant medical illness -H. pylori infection	0	Rabeprazole 0.5 mg or 1 mg once daily orally

				body weight of 10 kg	-sensitivity to PPI's		
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## OUTCOMES MEASURED

The outcomes measured in this study were the presence and severity of treatment-emergent adverse events (TEAE's) related to the use of Rabeprazole.<sup>1,2,3</sup> The patients involved in each of these studies were assessed at each study visit for TEAE's. These assessments included physical examinations, vital signs, 12-lead ECG, and lab tests such as hematology, chemistry, and urinalysis were done.<sup>1,2,3</sup> Most of the TEAE's in this study were discovered through subjective reporting by the patients themselves.<sup>1,2,3</sup> Differences in frequency of treatment emergent signs and symptoms (TESS) between the two treatment groups were analyzed using the Fischer exact test and/or an appropriate nonparametric procedure.<sup>2</sup>

## RESULTS

This review examined three RCT's including children ages 1-16 with a known history of GERD and then compared the use of a low dose of Rabeprazole in the first part of each study to a higher dose of Rabeprazole in the second part of each study for the treatment of GERD. The results of all three studies was reported as dichotomous data and therefore allowed examiners to assess the safety of the medication and any adverse events.<sup>1,2,3</sup>

In the James study there were a total of twenty-four subjects that enrolled in and completed the study.<sup>2</sup> Those patients with evidence of other significant health conditions, pregnant/lactating patients, patients unwilling to refrain from smoking or drinking alcohol during the study, patients with drug allergies or sensitivities to PPI's, patients with significant

viral or bacterial infection within one month of the screening period, patients who have had definitive acid lowering surgery or previous esophageal or gastric surgery were excluded from the study.<sup>2</sup> The subjects were separated into two groups based on their ages (12 - <14 years and 14-16 years) and then randomized to receive either a 10 mg or 20 mg dose of Rabeprazole during the second part of this study.<sup>2</sup> Those subjects who fell into the 12- <14 years range were considered the control group and were given 10mg doses of Rabeprazole.<sup>2</sup> Those subjects who fell into the 14-16 years range were considered the experimental group and were given 20mg doses of Rabeprazole.<sup>2</sup> No deaths or serious adverse events (SAE's) were reported during this study, and there were also no adverse events which led to patients withdrawing from the study.<sup>2</sup> The incidence or CER of treatment emergent signs and symptoms in the control group was 50%.<sup>2</sup> The incidence or EER of treatment emergent signs and symptoms in the experimental group was 41.7%.<sup>2</sup> Headache (16.7%) and nausea (8.3%) were the most common adverse events reported by subjects in this study.<sup>2</sup> The incidence of TESS that were considered to be related to the study were not however, considered to be clinically significant by the examiners.<sup>2</sup> The relative risk ratio (RRR) was calculated to be -16.6%.<sup>2</sup> This means that those subjects in the experimental group taking the higher dose of Rabeprazole have a 16.6% higher risk of developing an adverse event versus those in the control group taking the lower dose. The absolute risk reduction (ARR) was calculated to be -8.3%.<sup>2</sup> This means that of those taking in the experimental group taking the higher dose of Rabeprazole, 8.3% more will develop an adverse event compared to those in the control group taking the lower dose. The numbers needed to harm (NNH) was calculated to be -12.<sup>2</sup> This means that for every 12 patients taking the higher dose of Rabeprazole, 1 fewer would experience an adverse event.

In the Haddad study, patient's ages ranged from 1-11 years of age.<sup>1</sup> The subjects were divided by weight into two cohorts; a low-weight cohort (6-14.9 kg) and a high weight cohort (>15 kg).<sup>1</sup> The low weight cohort was the control group and the high weight cohort was the experimental group. These patients were then randomized to receive 5-10 mg of Rabeprazole in the low-weight cohort and 10-20 mg of Rabeprazole in the high-weight cohort.<sup>1</sup> Those patients with H. Pylori infection and allergies to PPI's were excluded from the study.<sup>1</sup> The incidence or CER of TEAE's in the control group of this study was 77.5%.<sup>1</sup> The incidence or EER of TEAE's in the experimental group of this study was 74.7%.<sup>1</sup> The most common reported TEAE's were vomiting, cough, abdominal pain.<sup>1</sup> There were no trends of TEAE's or clinically relevant changes seen in this study.<sup>1</sup> The relative risk ratio (RRR) was calculated to be -3.6%.<sup>1</sup> This means that those patients in the experimental group taking the higher doses of Rabeprazole have a 3.6% higher risk of developing an adverse event versus those in the control group. The absolute risk reduction (ARR) was calculated to be -2.8, which represents that of those in the experimental group taking the higher dose of Rabeprazole, 2.8% more will develop an adverse event compared to those in the control group taking the lower dose. The numbers needed to harm (NNH) was calculated to be -35.<sup>1</sup> This means that for every 35 patients taking the higher dose of Rabeprazole, 1 fewer would experience an adverse.

In the Zannikos study, patient's ages ranged from 1-11 years of age.<sup>3</sup> "Eight patients received 0.14 mg/kg of Rabeprazole during part one of the study.<sup>3</sup> During part two of this study 11 patients were randomized to receive 0.5 mg/kg of Rabeprazole and 9 patients were randomized to receive approximately 1 mg/kg of Rabeprazole."<sup>3</sup> Patients with evidence of other significant health conditions, with H. Pylori infection, and those patients with sensitivity

or allergies to PPI's were excluded from the study.<sup>3</sup> There were no deaths reported during this study.<sup>3</sup> One patient withdrew from the study on day five; she was diagnosed with moderate viral gastritis on day four and developed a volvulus on day seven.<sup>3</sup> These events were not considered to be related to the study.<sup>3</sup> The incidence or CER of TEAE's in the control group of this study was 81.8%.<sup>3</sup> The incidence or EER of treatment TEAE's in the experimental group of this study was 77.8%.<sup>3</sup> "Most of the TEAE's were mild in severity and not considered to be related to the study drug."<sup>3</sup> Vomiting (10.7%) was the most commonly reported adverse event reported by subjects in this study.<sup>3</sup> There were no trends of TEAE's or clinically relevant changes seen in this study.<sup>3</sup> The relative risk ratio (RRR) was calculated to be -4.9%.<sup>3</sup> This means that those in the experimental group taking the higher doses of Rabeprazole have a 4.9% higher risk of developing an adverse event versus those in the control group who received the lower dose. The absolute risk ratio (ARR) was calculated to be -4% which means that of those in the experimental group taking the higher dose of Rabeprazole 4% more will develop an adverse event compared to those in the control group who took the lower dose.<sup>3</sup> The numbers needed to harm (NNH) was calculated to be -25. This means that for every 25 people taking the higher dose of Rabeprazole 1 fewer would experience an adverse event.

**Table 2. Treatment Effects**

STUDY	P-value	CER	EER	RRR	ARR	NNH
James	P = <0.001	42%	38%	-9.52%	-4%	-25
Haddad	P = <0.001	42%	38%	-9.52%	-4%	-25
Zannikos	P = <0.001	81.8%	77.8%	-4.9%	-4%	-25

## DISCUSSION

Rabeprazole is a proton pump inhibitor indicated for the use of duodenal ulcers, GERD, H. Pylori eradication, and hypersecretory conditions like Zollinger-Ellison syndrome.<sup>8</sup> Two off label uses of Rabeprazole include the maintenance of healing and prevention of Duodenal ulcers as well as the treatment and prevention of NSAID-induced ulcers.<sup>8</sup> The only contraindication to the use of Rabeprazole is if the patient has a hypersensitivity to Rabeprazole, substituted benzimidazoles, or any other component of the formulation.<sup>8</sup> There are several warnings/precautions regarding the use of Rabeprazole. "The use of PPI's may increase the risk of Clostridium difficile-associated diarrhea (CDAD), especially in hospitalized patients."<sup>8</sup> Because of this, it is recommended that patients use the lowest dose of the medication for the shortest duration appropriate for the condition being treated.<sup>8</sup> There is increased risk of osteoporosis-related bone fractures with PPI therapy.<sup>8</sup> It is recommended that those patients on high dose (multiple daily doses) or long-term therapy (one year or longer) should be monitored.<sup>8</sup> Also, PPI's are known to diminish the therapeutic effect of Clopidogrel and should be avoided in patients taking Clopidogrel.<sup>8</sup>

While Rabeprazole has been extensively studied in adults, these are the first studies published investigating the use of Rabeprazole in children ages 1-16 years old.<sup>1,2,3</sup> Prior to these studies, other PPI's were proven effective in this patient population, and therefore it was not ethical to include a placebo arm to assess the spontaneous response rate.<sup>1,2,3</sup> While this was a major limitation to these studies the association between an improved endoscopic score and improved clinical symptom score suggest that a placebo effect was not a major determining

factor in the outcomes.<sup>1,2,3</sup> No deaths were reported during any of these studies, and “no dose-response relation was observed with respect to TEAE’s”.<sup>1,2,3</sup> Overall the number and the rate of TEAE’s commonly associated with Rabeprazole treatment were similar across all of the dose groups.<sup>1,2,3</sup>

## **CONCLUSION**

This review and the chosen studies showed that Rabeprazole is a safe treatment for GERD in children 1-16 years of age. No serious or life-threatening adverse events were reported related to the use of Rabeprazole during these studies, and patient’s quality of life was improved. Further studies should be double-blinded studies and would be more beneficial if included a larger sample size. In the future, the development of a concrete scale for assessing the TEAE’s involved with the use of PPI’s would be beneficial. Also, future research should longer treatment durations to more definitively evaluate the benefits versus the risks of treating GERD with Rabeprazole in this younger population.

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