



# Texas Children's Hospital

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# BAYLOR COLLEGE OF MEDICINE

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# COPY

August 30, 2000

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Dear Dr. Talarico:

In my opinion, there is a significant need for further study of the treatment of GERD in infants. The currently available prokinetics often appear to be ineffective or only partially effective. PPI's and H<sub>2</sub> blockers appear to work very well in some infants, but not at all in others. Efficacy/dosing studies are especially needed for PPI's.

The designs for such studies should include dose ranging studies, but a placebo versus a PPI or H<sub>2</sub> blocker added to background therapy (including a prokinetic) would be useful. Infants should have some measure of reflux to enter such studies – either pH probe, UGI or scan. Clear-cut, repeated spitting during episodes of apnea, bradycardia, and failure to thrive might be acceptable, but documented reflux by any of the above tests would be better.

End points for apnea, bradycardia or near SIDS episodes would have to include cessation of symptoms or a marked decrease in the number of episodes. A pH study should be included pre and post treatment, realizing that it is not always helpful. While pH <4.0 is not seen in all infants who clearly have GERD, it would be important to document those infants whose pH is low before and/or after study drugs.

Endpoints for failure to thrive obviously include normal growth, however, many of these infants stop eating because of pain and discomfort and this response would also have to be measured clinically and by pH probe and or endoscopy. The latter would be especially important if symptoms persist while on treatment.

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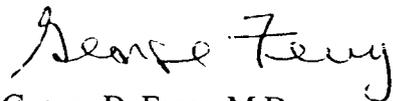
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Lilia Talarico, M.D.  
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Outcomes with asthma, aspiration and pneumonia will take 4-6 months to evaluate. Follow-up after treatment would be important to document recurrence of symptoms. Monitoring esophageal pH before and during treatment would be useful in these patients, as well.

I hope my comments are helpful and I look forward to the NASPGN and Children's Digestive Health and Nutrition Foundation workshop coming up in early December. Perhaps at that meeting there will be some consensus reached regarding needs and appropriateness of studies in infants.

Best wishes,



George D. Ferry, M.D.  
Professor of Pediatrics  
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GDF:lmg

July 31, 2000

George D. Ferry, M.D.  
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Dear Dr. Ferry:

Thank you for agreeing to provide further consultation to the Division of Coagulation and Gastrointestinal Drug Products regarding neonatal and infant use of acid reducing agents. Our division is evaluating whether there is a need for efficacy and safety studies in the neonatal and infant population for acid reducing agents used to treat supraesophageal/upper airway complications associated with gastroesophageal reflux disease (GERD). There appears to be widespread use of acid reducing agents in the neonatal and infant population related to complications of GERD including apnea, bradycardia, reactive airway disease, aspiration and failure to thrive. The relationship between reflux of acid and these clinical outcomes is unclear.

Before embarking on further discussions with sponsors, the Division is seeking the consultation of leaders in the field of infantile reflux to assist us in our assessment of the need for such studies and to obtain opinions on study design characteristics.

#### Background

Esophageal reflux in infancy is a common occurrence. It has been estimated that between 18-40% of infants consulting a physician's practice have regurgitation as a stated "complaint." Prevalence of pH-metric criteria for excessive reflux in this population has been estimated to be in the range of 8%. A recent survey of neonatal intensive care units (NICU) revealed that approximately 20% of patients in these units have been treated with cisapride and 50% of these infants have been discharged from the NICU on cisapride therapy.

Pathologic regurgitation (GERg) is differentiated from "physiologic or normal" regurgitation by the presence of associated clinical complications such as aspiration, wheezing, apnea, bradycardia, failure to thrive and feeding problems. Treatment for trivial or "normal" regurgitation or mildly abnormal amounts of regurgitation that troubles parents have included feeding thickening, smaller feedings, positioning and if the symptoms are bothersome enough, off-label use of prokinetics and histamine<sub>2</sub>-receptor antagonists. In the medical literature and in discussions with pediatric gastroenterology consultants, proton pump inhibitors (PPIs) are used in the most severe cases when diet, positioning, H<sub>2</sub> receptor antagonists and prokinetic agents have failed. They are avoided by some physicians due to the perceived risks associated with profound acid suppression, hypergastrinemia and potential genotoxicity that is present in vitro assays. The efficacy and safety of these empiric approaches has not been well characterized. The vast majority of cases of infantile GERD are self-limited (creating a problem in studies that have no control).

There is debate in the pediatric literature regarding the pathophysiology of infantile complications of GERD. Many authors assume that the volume of refluxate, unrelated to pH is related to clinical illness rather than acid content. Other authors raise the possibility that neurological mediated responses to acid in the esophagus or upper airways may cause cardiac and respiratory reflexes that result in life threatening apnea and bradycardia. The widespread use of acid reducing agents in this setting indicates that the possibility of acid related etiology is widely accepted.

PPIs are used in early infancy. A recent, well-referenced article reviewed safety and efficacy data in the medical literature.<sup>1</sup> This review documents the widespread usage of PPIs in children and infants. The role of PPIs relative to H<sub>2</sub> antagonists and prokinetics has not been studied in a way to allow for therapy based on rigorous science. There are no adequate and well-controlled studies in the literature of efficacy in the population of severe GERD or in subjects with respiratory compromise associated with GERD under the age of 1 year. The recent decision by Janssen to voluntarily cease marketing of cisapride highlights the need for adequate studies to evaluate the role of other modalities to treat infantile severe reflux (associated with respiratory compromise, bradycardia, failure to thrive and esophageal complications such as esophagitis).

Reference: Buck LM. Using proton pump inhibitors in children. *Pediatric Pharmacotherapy* ; 1999; 5 (4)

#### Questions:

1. Is there a need in the medical community for safety and clinically relevant efficacy information on the current pharmacologic therapy for complicated infantile GERD?
2. Specifically, is there a need for efficacy studies of PPIs, H<sub>2</sub> antagonists and/or prokinetics?
3. What general designs would be most appropriate?
  - a. placebo versus PPI added to "current standard", (e.g. placebo-controlled study on top of background standard of care therapy)
  - b. multidose single agent (dose ranging or comparison)
  - c. combination therapy multi-arm
  - d. PPI versus prokinetic and or H-2 receptor antagonist (active treatment control)
  - e. active run in with randomized placebo controlled withdrawal (randomized withdrawal)
  - f. other thoughts
4. What eligibility criteria should be used to define the study population?
5. Which study endpoints would be most appropriate?
  - a. apnea, bradycardia, near SIDS episodes associated with GERD
  - b. outcomes in failure to thrive associated with GERD
  - c. outcomes in infants with asthma, aspiration or pneumonia associated with GERD
  - d. surrogate endpoints
  - e. other thoughts