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Famotidine for infant gastro-oesophageal reflux: a multi-centre, randomized, placebo-controlled, withdrawal trial

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SUMMARY

Background: Gastro-oesophageal reflux afflicts up to 7% of all infants. Histamine-2 receptor antagonists are the most commonly prescribed medications for this disorder, but few controlled studies support this practice.

Aim: To evaluate the safety and efficacy of famotidine for infant gastro-oesophageal reflux disease.

Methods: Thirty-five infants, 1.3–10.5 months of age, entered an 8-week, multi-centre, randomized, placebo-controlled, two-phase trial: first 4 weeks, observer-blind comparison of famotidine 0.5 mg/kg and famotidine 1.0 mg/kg; second 4 weeks, double-blind withdrawal comparison (safety and efficacy) of each dose with placebo.

Results: No serious adverse events were reported. Eleven patients had 16 non-serious, possibly drug-related adverse experiences: 6 patients with agitation or irritability (manifested as head-rubbing in two), 3 patients with somnolence, 2 patients with anorexia, 2 with headache, 1 patient with vomiting, 1 patient with hiccups, and 1 patient with candidiasis. Of the 35 infants, 27 completed Part I. There were significant score improvements for famotidine 0.5 mg/kg in regurgitation frequency ($P = 0.04$), and for famotidine 1.0 mg/kg in crying time ($P = 0.027$) and regurgitation frequency ($P = 0.004$) and volume ($P = 0.01$). Eight infants completed Part II on double-blind treatment, which was insufficient for meaningful comparisons.

Conclusions: Histamine-2 receptor antagonists may cause agitation and headache in infants. A possibly efficacious famotidine dose for infants is 0.5 mg/kg (frequency adjusted for age). As 1.0 mg/kg may be more efficacious in some, the dosage may require individualization based on response. Further sizeable placebo-controlled evaluations of histamine-2 receptor antagonists in infants with gastro-oesophageal reflux disease are warranted.

INTRODUCTION

Gastro-oesophageal reflux disease (GERD) afflicts about 7% of all infants during their first year of life to the extent that they are brought to medical attention.[1]

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However, optimal therapy for infantile GERD remains inadequately defined. Indeed, efficacy data for 'lifestyle' measures (such as the effect of thickening of feed on the regurgitation frequency or of positioning on pH probe-identified acid reflux) are considerably stronger than most data for pharmacological therapies.[2, 3]

Extrapolating from GERD in adults, for whom acid suppression improves symptoms, pH probe variables and endoscopic findings, histamine-2 receptor antagonists (H_2RAs), particularly cimetidine and ranitidine, have been widely used in children, including infants,[4, 5] sometimes in association with a prokinetic agent.[6, 7] However, controlled data supporting the clinical efficacy of H_2RAs in infants are limited;[8] until now, the US Food and Drug Administration (FDA) has not approved any H_2RA for this use. Proton pump inhibitors, providing more complete acid suppression, have also been used for infantile GERD,[9] but it remains unclear whether such aggressive acid suppression is warranted for such young children, whose milk meals buffer the gastric contents for as much as 2 h after each of their multiple daily feeds.

Placebo-controlled trials of famotidine (US Adopted Name; Investigational Non-Proprietary Name) have shown improvement in symptoms and endoscopic findings in adults,[10, 11] and famotidine is approved by the FDA for use in adults with symptomatic GERD, erosive oesophagitis, active duodenal or gastric ulcer and for the maintenance of healed duodenal ulcer. Because famotidine was the first H_2RA licensed for paediatric use in children older than 12 months (for GERD and peptic ulcer disease), it is a logical H_2RA to evaluate in infants younger than 12 months with GERD.

The clinical pharmacokinetics and pharmacodynamics have been explored in adults,[12, 13] children[14–17] and infants.[18] The lack of drug interactions and the decreased frequency of administration allowed by its prolonged duration of action in young infants represent potential therapeutic benefits in this age group.[18]

This study was planned as a multi-centre, randomized, double-blind, placebo-controlled, withdrawal trial evaluating famotidine as therapy for symptomatic GERD in infants younger than 12 months of age. It was designed in accordance with the FDA written request for Famotidine Pediatric Studies (December 21, 1999) and a subsequent amendment (June 8, 2000).

METHODS

Subjects

Between January 27 and April 19, 2000, infants were recruited by investigators at three US sites to participate in the 8-week study, which had been approved by the institutional review board or human rights committee at each institution.

Inclusion criteria included a clinical diagnosis of GERD, an expected requirement for treatment of at least 8 weeks, an age of 0–12 months at enrolment, a gestational age at birth of ≥ 32 weeks, assessed ability (by investigator and nurse co-ordinator) to comply with the protocol and informed consent from a parent or guardian. The clinical diagnosis of GERD was made for each infant by the enrolling investigator, but, during analysis, the subjects were compared and contrasted symptomatically with infants with objective diagnoses of GERD and with normal infants to validate the subjects' diagnoses, as indicated in the Results section.

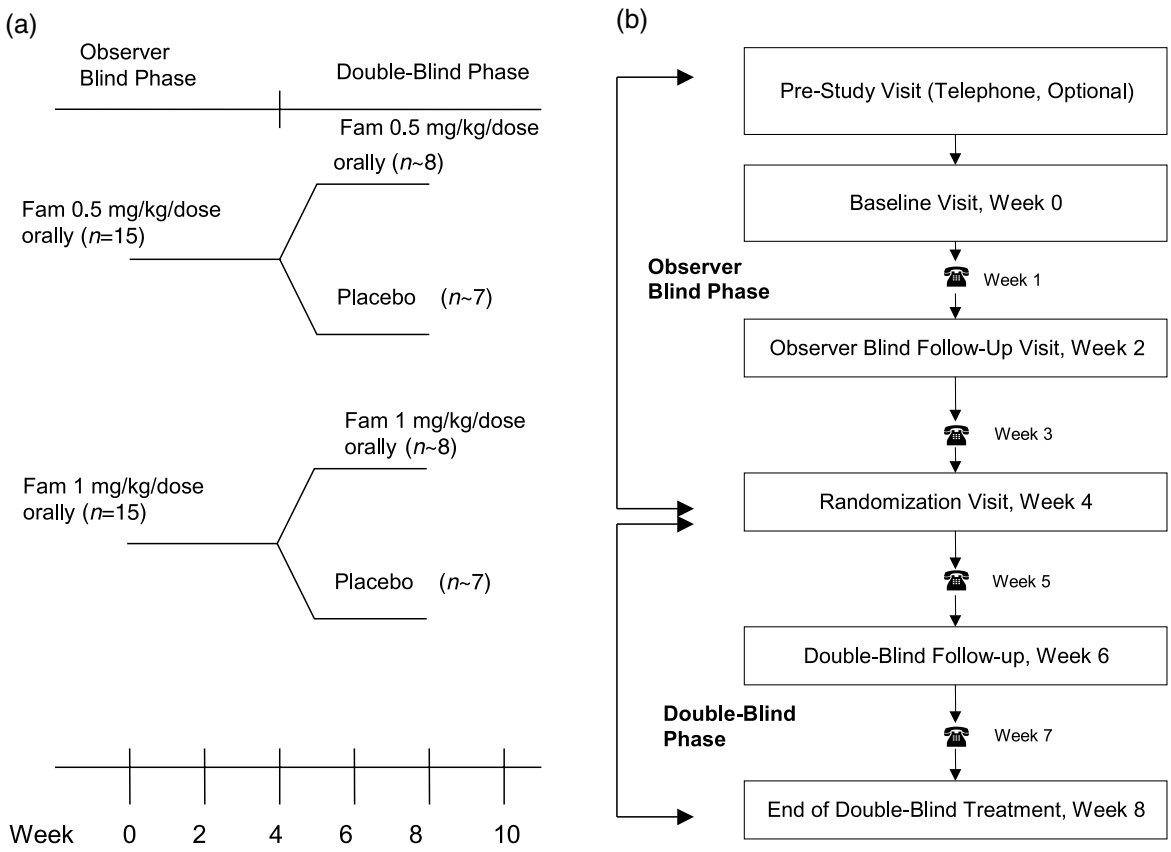
Exclusion criteria included a respiratory complication of GERD (including an apparent life-threatening event), a history of gastrointestinal surgery, unstable renal, cardiovascular, hepatic, neoplastic or diabetic disease, a history of any illness that might confound the results of the study or pose additional risk to the patient, an inability to discontinue previous proton pump inhibitor, H_2RA, antacid or prokinetic agent (required washout of ≥ 3 days) and a known hypersensitivity to famotidine or other H_2RA.

At least 30 babies were expected to 'complete' the study, with completion defined as treatment for at least 2 weeks, or discontinuation due to a lack of efficacy or to an adverse experience.

Design

The primary objective was to evaluate the safety and tolerability of famotidine administered for up to 8 weeks. The secondary exploratory objective was to evaluate the clinical efficacy of famotidine given for up to 8 weeks, measured as the alleviation of GERD symptoms (crying, regurgitation) and the improvement of global assessments (by parents/caregivers, physician); growth parameters were also measured.

The study was composed of two sequential parts as a randomized withdrawal trial to avoid subjecting symptomatic babies to the risk of placebo during their first weeks of participation (Figure 1a). Part I was a 4-week



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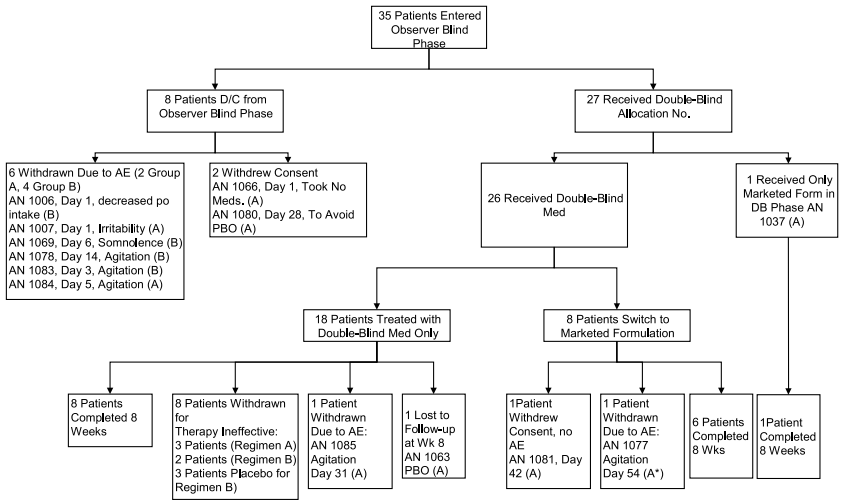

Figure 1. (a) Treatment diagram. The diagram illustrates the prospective study design, with anticipated numbers of patients (*n*) in each group. The observer-blind phase represents Part I and the double-blind phase represents Part II of the study. Fam, famotidine. (b) Study flow chart. The chart shows the sequence of study visits and telephone contacts. (c) Patient disposition. The diagram indicates the disposition of all 35 patients enrolled in the study. D/C, discontinued; AE, adverse event; A, famotidine 0.5 mg/kg dose regimen; B, famotidine 1.0 mg/kg dose regimen; po, oral; AN, allocation number (unique patient identification number); Med, medication; PBO, placebo; No., number; DB, double-blind.

trial in which infants were randomized to one of two (observer-blind) dosage levels of famotidine: 0.5 mg/kg and 1.0 mg/kg. Part II was a double-blind withdrawal trial during the subsequent 4 weeks in which the infants were randomized to continue treatment with the same dose of famotidine or to withdraw to placebo. The randomization for allocation to dose in Part I was distinct from the randomization for allocation to placebo in Part II. Enrolment in the double-blind phase (Part II) was stratified according to the regimen assigned at baseline. The investigator and study co-ordinator at each site were blind to the dose assignment during the first 4 weeks (Part I) and to active/placebo and dose assignment during the second 4 weeks (Part II); during Part I, blinding was maintained by employment of a study drug co-ordinator at each site who dealt with aspects that could impair blinding. The parents were blind to active/placebo assignment during the second 4 weeks.

Parents of all infants were instructed in conservative anti-reflux measures: normalization of feeding volume and frequency, and thickening of feeds with one tablespoon of dry rice cereal per ounce of formula. Concomitant medication with proton pump inhibitors, antacids, anticholinergic agents, prokinetic agents or other H_2RAs was proscribed.

Infants were evaluated at out-patient visits every 2 weeks (Figure 1b). During the weeks in which they did not visit the clinic, the study drug co-ordinator contacted the families by telephone to support compliance with the protocol and to detect adverse events most effectively. The four bi-weekly out-patient follow-up visits were used to obtain efficacy data. The study drug co-ordinator also collected dose diaries and the pharmacist weighed returned drugs to assess compliance with the protocol and to track drug disposition during the sequence of 10 visits and telephone contacts. At week 0, informed consent, history, Infant Gastro-oesophageal Reflux Questionnaire, vital signs and laboratory data were obtained; laboratory data were repeated at week 8, or at discontinuation from the study if it occurred before 8 weeks. At each subsequent clinic visit, the study co-ordinator collected symptom diaries (and dispensed new ones) and assessed GERD symptoms, and the study drug co-ordinator collected medications and diaries (and dispensed new ones).

The study was originally designed to accept babies requiring intravenous therapy as well as those able to take famotidine suspension orally. None of the recruited babies required intravenous therapy during the study, and therefore this portion of the protocol will not be discussed further.

Dosing and drug formulation

Based on previous evaluations of famotidine pharmacokinetics and pharmacodynamics in infants and children,[14, 18] and following consultation with the FDA, the two oral dosages evaluated were 0.5 and 1.0 mg/kg, given as a suspension. Oral dosing recommendations in children older than 12 months are similar to those for adults: 0.5 mg/kg daily at bedtime is used for peptic ulcer.[19] The renal maturation that occurs at 3 months of age mandated the administration of the assigned dose once daily in babies younger than 3 months and twice daily in those 3 months and older.[18] At the second visit (conclusion of week 2), infants assigned to the lower dose (0.5 mg/kg), whose therapy was ineffective and who would therefore otherwise not be continuing, had the option of continuing on the 1.0 mg/kg dose. The dosage of famotidine (or placebo) during Part II was the dosage used for that baby during the second 2 weeks of Part I.

The study was initiated with oral famotidine and matching placebo prepared as a suspension. The drug dose (in mL) was recalculated every 2 weeks by the study drug co-ordinator and checked by the pharmacist after the babies had been weighed at the clinic visits.

On April 21, 2000, the protocol was amended to discontinue treatment of the remaining patients with the investigational oral famotidine formulation and matching placebo because of a degradate that formed when famotidine for oral suspension was reconstituted with the vehicle used to make the placebo and famotidine indistinguishable for the study. Patients who continued ($n = 9$, including those who had been assigned to active drug and those who had been assigned to placebo) were treated with active marketed famotidine oral suspension to eliminate their exposure to the degradate.

Safety and tolerability assessment

At each clinic visit, symptomatic adverse events were recorded and rated by the investigator with regard to intensity (mild–easily tolerated, moderate or severe–incapacitating) and drug relationship (definitely not, probably not, possibly, probably, definitely). Parents were also asked about symptomatic adverse events at each weekly interval telephone contact. At each visit,

physical examination and vital sign monitoring provided scheduled data for adverse event assessment. Phlebotomy and urine collection for haematology (complete blood count), chemistry (aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase) and creatinine clearance were evaluated at specified visits and at other times if deemed necessary by the investigators, who interpreted the clinical significance of any abnormal results.

Efficacy assessment

At baseline, the parents or caregiver completed the Infant Gastro-oesophageal Reflux Questionnaire, and at subsequent visits they completed a shortened version quantifying the symptoms of crying duration, regurgitation frequency and regurgitation volume during the 2-week interval. Parents/caregivers and investigators also independently completed global assessments (completely well, somewhat improved, not at all improved, worse) of progress during the 2-week interval. Bi-weekly measurements of nude weight, length (via stadiometer) and head circumference characterized growth.

Statistical analysis and power

The sample size of about 30 babies was determined in accordance with an FDA written request for famotidine paediatric studies. The power of the study to disclose adverse events, the primary objective of the study, based on the actual number of patients enrolled in each of the two dosage groups, 18 and 17, is such that an observed incidence of an adverse event of zero produces a 95% confidence interval (CI) for the true incidence rate of ≤ 0.162 and ≤ 0.153 at the two dosages. Similarly, an observed incidence of four adverse events produces a 95% CI upper limit for the true incidence rate of ≤ 0.5 for both dosages.

For the analysis of safety in Part I, subjects were grouped by their 'intention-to-treat' dosage, i.e. the dose to which they were randomized (even if they required dose escalation); for the analysis of safety in Part II, they were grouped by the treatment actually received. Adverse events were summarized by phase (Part I or II), and Fisher's exact test was used for comparisons.

Efficacy analysis, an exploratory objective of the study, used a modified intention-to-treat approach, evaluating all subjects who had at least one post-baseline (i.e. 2-week) efficacy assessment for either Part I or II. For efficacy analyses, patients were grouped for each phase according to the treatment assigned, even if the dose was increased at week 2. For Part I, changes from baseline were assessed within each of the two dosage levels by the marginal homogeneity test for reflux symptoms, or Wilcoxon signed rank test for the measures of growth, and differences between the two groups were assessed by the Wilcoxon rank sum test. For Part II, within-group comparisons were made with respect to the change from the 'baseline' data from week 4, and between-group comparisons were made between each of the two dosage levels and their respective placebos.

There were no non-pre-specified exploratory analyses and no interim analyses performed. Missing data were left as missing and excluded from the statistical analysis. Missing data particularly impacted on the Part II data after the protocol amendment switched many subjects from the investigational drug or placebo to marketed famotidine. Data from unscheduled visits were used instead of those from subsequent scheduled visits, if the subsequent visit did not occur (e.g. because of premature discontinuation from the study).

RESULTS

Subjects

A total of 35 infants were enrolled (median age, 5.3 months; range, 1.3–10.5 months); 57% were female and 91% were white. Figure 1(c) (patient disposition) and Table 1 (patient characteristics and results) characterize and account for the subjects. The babies' symptomatic reflux was indicated by the proportion (> 60%) with excessive values for crying duration (> 1 h/day), regurgitation frequency (> 3 times/day) and regurgitation volume (> 1 tablespoon/episode), values found in < 20% of normal babies.[20] It was further characterized by an Infant Gastro-oesophageal Reflux Questionnaire score distribution (Figure 2a) characteristic of infants who had objective (pH probe or biopsy) evidence of GERD at a tertiary care centre, and in contrast with normal infants undergoing well baby care (Figure 2b[20]). Finally, the strength of the clinical diagnosis of GERD made prior to consideration for inclusion in the study was supported by the previous prescription of H_2RAs (57%) or prokinetic agents (37%) to a substantial number of the infants, with similar proportions assigned to each treatment group.

Table 1. Patients: characteristics and results. Patient characteristics and accounting during Part II of the study, showing efficacy results at conclusion of Part II (Impr, improved; NC, no change; or worse) and other disposition (lost to Part II because of adverse event, ineffectiveness or other; or switched by amendment to marketed famotidine)

	Fam 0.5 ($n = 8$)	Fam 1.0 ($n = 7$)	P 0.5 ($n = 5$)	P 1.0 ($n = 6$)	Total ($n = 26$)
Age (median, range, months)	6.6, 1.7–10.2	3.7, 1.3–10.5	4.7, 2.2–8.5	7.6, 1.8–10.2	5.5, 1.3–10.5
Sex (n) (male : female)	3 : 5	2 : 5	2 : 3	5 : 1	12 : 14
Patient accounting					
Completed Part II	2	2	1	3	8
Cry: Impr/NC/worse	0/1/1	0/2/0	0/0/1	2/0/1	2/3/3
Spit freq.: Impr/NC/worse	0/2/0	1/0/1	0/1/0	1/1/1	2/4/2
Spit vol.: Impr/NC/worse	0/1/1	1/1/0	0/0/1	1/2/0	2/4/2
Global — parent: Impr/NC/worse	0/2/0	1/1/0	0/1/0	2/0/1	3/4/1
Global — physician: Impr/NC/worse	2/0/0	1/1/0	0/1/0	2/0/1	5/2/1
Discontinued Part II	4	2	2	2	10
Adverse event (agitation)	1	0	0	0	1
Ineffective	3	2	0	3	8
Lost to follow-up	0	0	1	0	1
Switched (by amendment)	2	3	2	1	8

Fam 0.5, famotidine 0.5 mg/kg; Fam 1.0, famotidine 1.0 mg/kg; P 0.5, placebo 0.5 mg/kg; P 1.0, placebo 1.0 mg/kg.

All patients had at least one other diagnosis during the study, with otitis media (8/35), respiratory infections (3/35), oral candidiasis (3/35) and mild skin rashes (3/35) being most common. Seventy-one per cent of patients had received previous pharmacotherapy: 57% had received previous H_2RA (cimetidine or ranitidine) or sucralfate therapy, and 37% had previously received a prokinetic agent (cisapride or metoclopramide). Two-thirds received concomitant pharmacotherapy during the study: 31% acetaminophen, 11% ibuprofen and 31% antibiotics.

Thirty-four of the 35 infants 'completed' as defined above; 27 completed all 4 weeks of Part I, and 26 of these participated in Part II (Figure 1c). Protocol violations were documented for three subjects, one of whom took Mylanta for 5 days before the week 4 visit, and two of whom discontinued after < 3 days in the study for adverse events, and thus did not have any scheduled visit data. All randomized patients were included in the safety analyses. There were no identifiable differences between the patients recruited or the results of treatment in the three study sites. There were no age-related differences in response to treatment or withdrawal. Therefore, the analysis was performed without distinguishing between the sites or between infants of different ages.

Tolerability and safety

Clinical adverse events. There were no serious adverse events. Most patients in all treatment groups had at least one adverse event, but most were intercurrent illnesses (e.g. otitis, upper respiratory infection, pharyngitis). These illnesses were reflected in the concomitant pharmacotherapy (antibiotic and antipyretic) taken during the study, and were expected by the babies' ages and the winter–spring season.

Throughout the study, 11 patients (nine observer-blind to the dose during Part I, one double-blind during Part II and one observer-blind both in Part I and after switching to the marketed drug) had adverse events assessed by an investigator as possibly, probably or definitely drug related; four of these were initially randomized to receive famotidine 0.5 mg/kg and seven were randomized to receive 1.0 mg/kg (P = N.S.). Ten of the 11 adverse events interpreted as being possibly drug related occurred whilst patients were known to be taking active drug. Eight of these (four at each dosage) discontinued because of these non-serious adverse events: six during Part I, one during Part II and one during the marketed famotidine phase. (Thus seven of the eight who discontinued for an adverse event were known to be taking active drug.) When adverse events were compared between the doses without regard to the investigator assessment of drug relatedness, 72% of those on 0.5 mg/kg and 100% of those on 1.0 mg/kg had an adverse event ($P = 0.045$).

Six babies experienced adverse events described as new agitation or irritability, four of which occurred within the first week of treatment and five of which resolved within a few days after the withdrawal of famotidine.

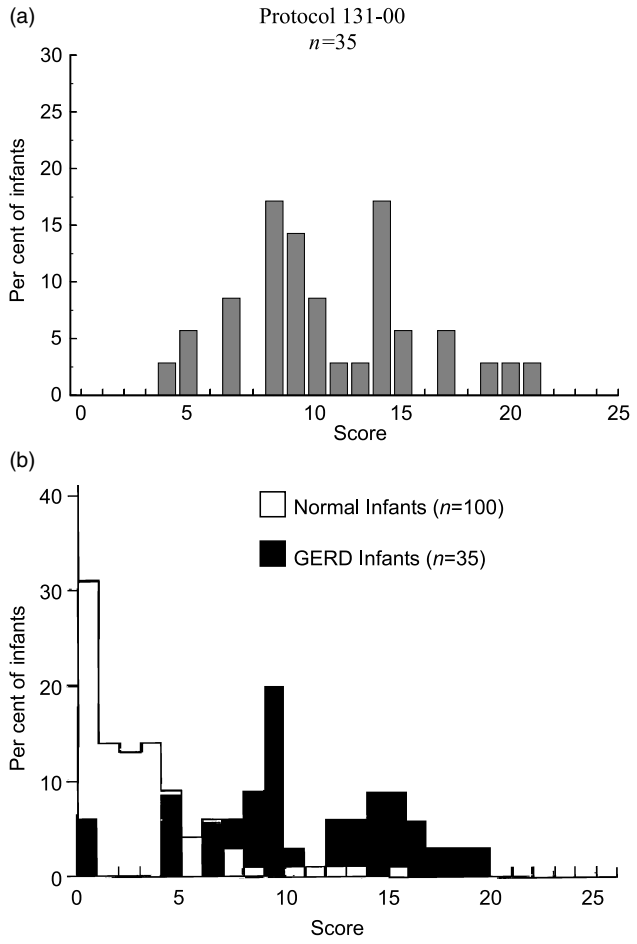

Figure 2. (a) Distribution of Infant Gastro-oesophageal Reflux Questionnaire (I-GERQ) scores at baseline. These scores are similar in distribution to those of 35 other infants with gastro-oesophageal reflux disease (GERD) (documented by pH probe or histology to have GERD in a previous study validating I-GERQ scores) and contrast with the distribution of scores in 100 normal infants from the same study (b).[20] (Figure 2b reproduced with permission.)

The symptoms were described as excessive crying and fussing, accompanied in at least two of the babies by head rubbing, interpreted by parents as suggesting a headache.

During the study, severe symptoms of GERD were sought prospectively, including apnoea, choking or other signs of aspiration, in order to identify severe adverse sequelae of inadequate therapy, allowing the progression of disease. No baby experienced clinically significant apnoea, bradycardia or aspiration. The parents of six babies (five on 1.0 mg/kg and one on 0.5 mg/kg) identified 'gagging/choking' or 'difficulty breathing' in the symptom diaries; they were generally brief and none prompted withdrawal from the study. Four parents documented three or fewer episodes of gagging/choking lasting for 1 min or less each. A fifth baby, with a pre-study history of apnoea and occasional noisy breathing, was cited as experiencing 15 episodes of gagging/choking or difficulty breathing, largely during a 2-week interval in the midst of the study. A sixth baby had a single episode of difficulty breathing lasting for 30 min on the second day after enrolment, which was related to the onset of an upper respiratory illness.

Laboratory adverse events. Four patients had laboratory adverse events: two on 0.5 mg/kg and two on 1.0 mg/kg. These were all asymptomatic neutropenia detected at routine phlebotomy at the conclusion of treatment. Absolute neutrophil count nadirs ranged from 380 to 1180. All recovered to normal levels. Although these were considered at the time to be possibly drug related, they occurred at a similar frequency in the famotidine and placebo groups, and haematology consultation assessed them as likely to be related to intercurrent viral illnesses.

Clinical and laboratory safety measurements. The famotidine and placebo groups did not differ with regard to growth or the distribution of patients across pre-treatment and post-treatment laboratory measures.

Efficacy (Figure 3, Table 1)

Crying. In the 0.5 mg/kg group, although about one-third of babies improved their crying scores, the distribution of the crying scores did not differ significantly from baseline at weeks 2 and 4, while the investigators remained blind to the dose. This was in contrast with the 1.0 mg/kg group, in which two-thirds of babies improved from baseline to 4 weeks ($P = 0.027$), most having improved by week 2 ($P = 0.018$). The improvement from baseline in the 1.0 mg/kg group was not reflected in statistically different crying scores from the 0.5 mg/kg group at 2 weeks or 4 weeks of treatment, perhaps because the 1.0 mg/kg group had worse crying scores at baseline. (At baseline, 50% of babies in the 0.5 mg/kg group cried > 1 h/day, but 69% of those in the 1.0 mg/kg group did so.) During Part II, the double-blind phase, when one-half of the babies in each group were withdrawn to placebo, there were no significant differences

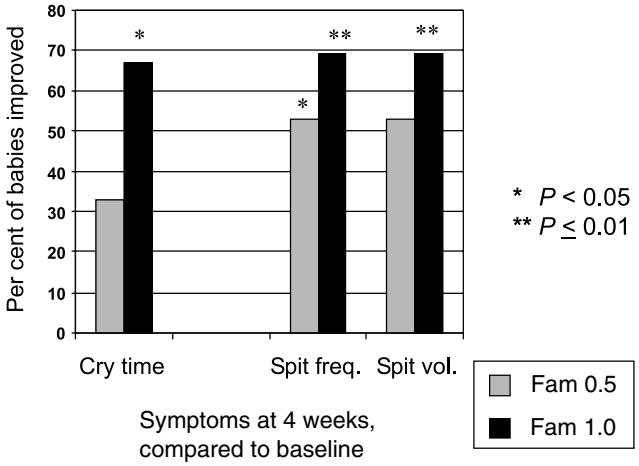

Figure 3. Results: efficacy — Part I. Improvement in crying time, regurgitation (possetting) frequency ('Spit freq.') and regurgitation volume ('Spit vol.') during the 4-week observer-blind phase of the study.

in crying scores; however, the small numbers in each of the four groups, exaggerated by the amendment that switched subjects to the marketed drug, prompts caution in drawing conclusions from Part II. (This advisable caution, needed for all of the efficacy variables, will be identified in subsequent paragraphs as 'small numbers caution'.)

Regurgitation frequency. During Part I, with observers blind to the dose, the majority of babies in both dosage groups improved from baseline to week 2 (50% for 0.5 mg/kg, $P = 0.023$; 81% for 1.0 mg/kg, $P = 0.001$) and week 4 (Figure 3: 53% for 0.5 mg/kg, $P = 0.040$; 69% for 1.0 mg/kg, $P = 0.004$). No statistically significant differences in this parameter were observed between the two doses. During Part II, the double-blind phase, there were no significant differences between active drug and placebo in regurgitation frequency at either dose level (small numbers caution).

Regurgitation volume. At baseline, 75% of babies in the 0.5 mg/kg group regurgitated > 1 tablespoon/episode, and 69% of those in the 1.0 mg/kg group did so. However, 50% of babies in the 1.0 mg/kg group regurgitated > 1 oz/episode (compared to 37% of those in the 0.5 mg/kg group), and 6% of babies in the 1.0 mg/kg group were characterized by their parents as regurgitating 'the whole feed', whereas none of those in the 0.5 mg/kg group did so. These differences were not statistically significant. In both dosage groups, the majority of babies improved from baseline to week 2 and week 4, but these improvements only reached significance for the 1.0 mg/kg group, in which 69% improved at week 2 ($P = 0.012$) and 69% improved at week 4 ($P = 0.010$) (Figure 3). During Part II, the double-blind phase, there were no significant differences between active drug and placebo in regurgitation volume at either dose level (small numbers caution).

Global assessment — parent. In Part I, while babies were known to be on active drug, the majority of parents assessed their child as improved (including 'completely well') in each of the dosage groups from baseline to week 2 (88% for the 0.5 mg/kg group and 94% for the 1.0 mg/kg group), and from week 2 to week 4 (63% for the 0.5 mg/kg group and 69% for the 1.0 mg/kg group). Some of these were deemed to be 'completely well' at week 2 (6% in the 0.5 mg/kg group and 19% in the 1.0 mg/kg group) and at week 4 (13% in the 0.5 mg/kg group and 25% in the 1.0 mg/kg group). There were no significant differences between the dosage groups either at 2 weeks or at 4 weeks. During Part II, the double-blind phase, there were no significant differences between active drug and placebo in parent global assessment at either dose level (small numbers caution). Of the 15 babies who completed 8 weeks of the study (blind famotidine, four; blind placebo, four; marketed famotidine, seven), five were deemed to be completely well; one of these was on blind famotidine, and the rest were on unblind marketed famotidine. Three other babies discontinued the study medication prior to 8 weeks, with parent global assessments of 'completely well': two were taking marketed famotidine and one was taking blind placebo.

Global assessment — physician. In Part I, while babies were known to be on active drug, the investigators assessed the majority of babies as improved in each of the dosage groups from baseline to week 2 (88% for the 0.5 mg/kg group and 94% for the 1.0 mg/kg group), and from week 2 to week 4 (63% for the 0.5 mg/kg group and 75% for the 1.0 mg/kg group). Some were deemed to be 'completely well' at week 2 (6% at both dosage levels) and at week 4 (13% for the 0.5 mg/kg group and 25% for the 1.0 mg/kg group). There were no significant differences between the dosage groups at either 2 weeks or 4 weeks. During Part II, the double-

blind phase, there were no significant differences between active drug and placebo in the physician global assessment at either dose level (small numbers caution). Of the 15 babies who completed 8 weeks of the study (blind famotidine, four; blind placebo, four; marketed famotidine, seven), seven were deemed to be 'completely well'; one of these was on blind famotidine, one on blind placebo and the rest on unblind marketed famotidine. Three other babies discontinued the study medication prior to 8 weeks, with physician global assessments of 'completely well': two were taking marketed famotidine and one was taking blind placebo.

Discontinuation for ineffective therapy. During the double-blind phase, no patients were withdrawn due to ineffective therapy. During the withdrawal phase, eight patients were withdrawn due to ineffective therapy, three whilst taking 0.5 mg/kg famotidine, two whilst taking 1.0 mg/kg famotidine and three whilst taking placebo.

Growth. There were no significant differences between the two dosage groups or between active drug and placebo in any measure of growth during the 8-week study.

DISCUSSION

This is one of the largest multi-centre, randomized, double-blind, placebo-controlled studies evaluating an H_2RA in infants, a group commonly treated with such medications. In general, it indicates the safety and tolerability of famotidine in infants, although it suggests that agitation, possibly representing headache, might be a side-effect in infants. Efficacy is suggested by the improvement in regurgitation frequency in both dosage groups at 2 weeks and 4 weeks, and by the improvement in regurgitation volumes and crying duration in the higher dosage group at both 2 and 4 weeks, when the babies were known to be on active drug. The placebo-controlled withdrawal phase of the study did not demonstrate the efficacy of the drug compared to placebo.

The diagnosis of GERD in these infants was symptom based, as is increasingly the case in clinical practice for infants as well as adults with GERD. The diagnosis was supported in these babies by their scores on a questionnaire previously validated for this diagnostic purpose, by their paediatricians' referral for this diagnosis, by their paediatricians' decision to use pharmacotherapy for GERD prior to their referral in most cases and by their typical clinical course subsequent to the study. These methods of diagnosis increase the applicability of the study's results to other clinically diagnosed infants.

The side-effects of agitation, irritability and headache deserve comment. Headache, a known side-effect of all H_2RAs, was listed as an occasional side-effect on the consent form. Parents may thus have been stimulated to be alert to it. All of these adverse events were identified at one centre that enrolled 24 of the 35 patients in the study, and in babies known to be taking active drug. After they had been noted in one baby, attentiveness to them was increased.

Efficacy measures improved modestly during famotidine therapy in the non-placebo-controlled portion of the study, and did not improve significantly more than placebo in the placebo-controlled portion. However, the study was biased towards the failure of pharmacotherapy by the inclusion of patients who had previously failed treatment with H_2RAs (60%) or prokinetic agents (20%).[21]

The improvement in symptoms from baseline whilst babies were taking known active drug can be questioned on two bases. First, the natural history of babies with GERD is to improve during the first year of life. Second, any intervention will have an additional placebo effect. These are considerations that should prompt scepticism regarding any non-placebo-controlled study of a therapy for infantile GERD, leaving us with very few studies (of any therapy) that can confidently indicate efficacy for this disorder. If the observed improvement of symptoms in this study is actually due to therapy, the greater improvement at the higher dose makes intuitive sense.

The lack of a clear improvement, as measured by symptoms or the rate of withdrawal, in the placebo-controlled portion of the study can be attributed to the small numbers of babies in each group. These small numbers resulted from the limited numbers of infants available to participate in clinical trials, from the design of the study which fractionated the subjects by testing two doses against their placebos, from the previous discontinuation of some patients due to adverse events and from the amendment to the protocol that switched remaining babies to marketed drug because of an interaction between famotidine and the vehicle used to dilute it for the study. Expectation bias is an additional factor that may have limited the perceived

symptomatic improvement in this withdrawal design: many parents who were fairly confident that their babies would improve whilst on active drug expressed anxiety about the possible withdrawal to placebo, and anticipated a loss of efficacy.

The withdrawal design of the study was prompted by concern about placebo treatment for babies presenting symptomatically, because of the assumption that H_2RAs are effective in infantile GERD. The use of two dosage groups, arrived at in consultation with the FDA during the design of the study, which reduced the power to define efficacy at either dose, was prompted by a desire to clarify the optimal dose in infants.

The results of this study suggest a need for further sizeable placebo-controlled evaluations of H_2RAs in infants symptomatic with GERD, as it is unclear whether H_2RAs can be assumed to be efficacious for this age group in the absence of such studies. A simple, parallel-group, non-withdrawal design is justified by the lack of clarity about the efficacy of H_2RAs in infants with GERD. The results also suggest that agitation and symptoms indicative of headache should be sought prospectively in such studies. Finally, the results suggest that 4 weeks of treatment at a dosage of 0.5 mg/kg of famotidine (dose frequency adjusted for postnatal age) may be efficacious in infants when used as an adjunct to conservative measures, including thickened feeds. As 1.0 mg/kg may be more efficacious in some babies, however, the dosage may need to be individualized based on response.

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REFERENCES

1 Orenstein S. Gastroesophageal reflux. In: Hyman P, Di Lorenzo C, eds. Pediatric Gastrointestinal Motility Disorders. New York: Academy Professional Information Services, 1994: 55–88.
2 Shalaby TM, Orenstein SR. Efficacy of telephone teaching of conservative therapy for infants with symptomatic gastroesophageal reflux referred by pediatricians to pediatric gastroenterologists. J Pediatr 2003; 142: 57–61.
3 Carroll A, Garrison M, Christakis D. A systematic review of nonpharmacological and nonsurgical therapies for gastroesophageal reflux in infants. Arch Pediatr Adolesc Med 2002; 156: 109–13.
4 Kelly D. Do H2 receptor antagonists have a therapeutic role in childhood? J Pediatr Gastroenterol Nutr 1994; 19(3): 270–6.
5 Lambert J, Mobassaleh M, Grand R. Efficacy of cimetidine for gastric acid suppression in pediatric patients. J Pediatr 1992; 120(3): 474–8.
6 Galmische JP, Brandstatter G, Evreux M, *et al.* Control of severe reflux oesophagitis with combined cisapride–cimetidine treatment: a double-blind controlled trial. In: Johnson AG, Lux G, eds. Progress in the Treatment of Gastrointestinal Motility Disorders. The Role of Cisapride. Amsterdam: Excerpta Medica, 1988: 74–5.
7 Lieberman D, Keeffe E. Treatment of severe reflux esophagitis with cimetidine and metoclopramide. Ann Intern Med 1986; 104(1): 21–6.
8 Cucchiara S, Gobio-Casali L, Balli F, *et al.* Cimetidine treatment of reflux esophagitis in children: an Italian multicentric study. J Pediatr Gastroenterol Nutr 1989; 8(2): 150–6.
9 Alliet P, Raes M, Bruneel E, Gillis P. Omeprazole in infants with cimetidine-resistant peptic esophagitis. J Pediatr 1998; 132(2): 352–4.
10 Sabesin S, Berlin R, Humphries T, *et al.* Famotidine relieves symptoms of gastroesophageal reflux disease and heals erosions and ulcerations: results of a multicenter, placebo-controlled, dose-ranging study. Arch Intern Med 1991; 151: 2394–400.
11 Marrero J, de Caestecker J, Maxwell J. Effect of famotidine on oesophageal sensitivity in gastro-oesophageal reflux disease. Gut 1994; 35: 447–50.
12 Echizen H, Ishizaki T. Clinical pharmacokinetics of famotidine. Clin Pharmacokinet 1991; 21(3): 178–94.
13 Yeh KC, Chremos AN, Lin JH, *et al.* Single-dose pharmacokinetics and bioavailability of famotidine in man: results of multicenter collaborative studies. Biopharm Drug Dispos 1987; 8: 549–60.
14 James LP, Marshall JD, Heulitt MJ, Wells TG, Letzig L, Kearns GL. Pharmacokinetics and pharmacodynamics of famotidine in children. J Clin Pharmacol 1996; 36: 48–54.
15 Treem W, Davis P, Hyams J. Suppression of gastric acid secretion by intravenous administration of famotidine in children. J Pediatr 1991; 118(5): 812–6.
16 Kraus G, Krishna DR, Chmelarsch D, Schmid H, Klotz U. Famotidine. Pharmacokinetic properties and suppression of acid secretion in paediatric patients following cardiac surgery. Clin Pharmacokinet 1990; 18: 77–81.
17 Nagita A, Manago M, Aoki S, Mino M, Suzuli K, Ashida K. Pharmacokinetics and pharmacodynamics of famotidine in children with gastroduodenal ulcers. Ther Drug Monit 1994; 16(5): 444–9.

18 James LP, Marotti T, Stowe CD, Farrar HC, Taylor BJ, Kearns GL. Pharmacokinetics and pharmacodynamics of famotidine in infants. J Clin Pharmacol 1998; 38: 1089–95.
19 U.S. Package Circular: PEPCID® (Tablets for Oral Suspension and Orally Disintegrating Tablets). Whitehouse, NJ: November 1998.
20 Orenstein S, Shalaby T, Cohn J. Reflux symptoms in 100 normal infants. Diagnostic validity of the Infant Gastroesophageal Reflux Questionnaire. Clin Pediatr 1996; 35(12): 607–14.
21 Spilker B. Guide to Clinical Studies and Developing Protocols. New York: Raven Press, 1984: 1–302.