Archives of Disease in Childhood, 1984, **59**, 842–847

Antacids and cimetidine treatment for gastro-oesophageal reflux and peptic oesophagitis

S CUCCHIARA, A STAIANO, G ROMANIELLO, S CAPOBIANCO, AND S AURICCHIO

Pediatric Clinic, 2nd School of Medicine, University of Naples, Italy

SUMMARY Thirty three children aged 2 to 42 months (mean 9 months) with gastro-oesophageal reflux and peptic oesophagitis took part in a treatment trial comparing cimetidine (20 mg/kg/day) with an intensive regimen of antacids (Maalox, 700 mmol (mEq)/1·73 m^2/day). All children were evaluated clinically and by radiology, acid reflux test, and endoscopy. After 12 weeks of treatment all were again evaluated clinically, by pH measurement, and endoscopy. Twenty nine children, 15 on antacid and 14 on cimetidine, completed the trial. Eight patients on antacid and seven on cimetidine were cured; five on antacid and six on cimetidine improved; and two patients on antacid and one on cimetidine underwent surgery. Both groups of children showed a statistically significant reduction in the score of clinical, pH, and endoscopic variables after treatment. Lower oesophageal sphincter pressure before treatment did not correlate significantly with the final total score. Antacids in large quantities are as effective as cimetidine in medical treatment of gastro-oesophageal reflux and peptic oesophagitis.

There have been several recent studies of gastro-oesophageal reflux in children[1 2] but most reports deal with the clinical manifestations and diagnosis. Unlike studies in adults, controlled treatment trials of antacids, H_2 receptor blockers, cholinergic drugs, and dopamine antagonists have rarely been performed in children. Two recent trials with bethanechol, a cholinergic agent, suggest its usefulness in the treatment of children with gastro-oesophageal reflux.[3 4] These studies, however, did not evaluate the efficacy of the drug in peptic oesophagitis. We performed a controlled trial with liquid magnesium hydroxide and aluminum hydroxide (Maalox) and cimetidine in the treatment of children with gastro-oesophageal reflux and oesophagitis. Cimetidine and antacid were given in association with frequent, small feeds and positional treatment.

Patients and methods

Forty six children (29 boys and 17 girls) aged 2 to 58 months (mean 10·3 months) were referred to our department with an history suggesting gastro-oesophageal reflux. Diagnostic investigations included tests for infectious, neurologic, and metabolic diseases; roentgen study of the upper gastrointestinal tract; oesophageal manometry; pH probe test; and upper endoscopy. The latter was performed only if either radiological findings or pH measurements, or both, were positive for gastro-oesophageal reflux. All the investigations were undertaken after informed written consent had been obtained from the parents.

Gastro-oesophageal reflux was shown by means of radiology and acid reflux test (Tuttle test). Radiology was performed according to a technique previously described.[5] The roentgen study was considered positive for gastro-oesophageal reflux if at least two episodes of reflux were observed during fluoroscopy. This study was followed the next day by an oesophageal manometry performed with a three lumen catheter (polyvinylchloride tube, diameter 0·8 mm). Three distal side holes of diameter of 0·5 mm, 2·5 cm apart, and radially located at 120° were continuously perfused with bubble free water by a low compliant perfusion system at a rate of 0·6 ml/minute (Arndorfer Med Spec Inc, USA). The pressures were measured by connecting each lumen to a Statham P23D transducer and were recorded on a polygraph (Beckman type 611 R). Sudden occlusion of the distal side openings caused a pressure rise of at least 400 mmHg/second. Lower oesophageal sphincter pressure was determined as the average

mean pressure of three consecutive station pull-throughs with the gastric pressure as a zero reference. Oesophageal manometry was performed after a 6 hour fast and was followed by pH measurement after perfused water had been removed from the stomach. The acid reflux test in children (Tuttle test) has previously been described:[6 7] we used a small flexible pH electrode (MI-506, Microelectrodes Inc, USA). Gastro-oesophageal reflux was defined as a drop in intraluminal pH of below 4, for at least 20 seconds. Children with a diagnosis of gastro-oesophageal reflux on the basis of either radiology or pH study, or both, underwent upper endoscopy performed with a paediatric fibre endoscope (Olympus, GIF P2) 30 minutes after administration of promethazine (0·5 mg/kg intramuscularly) and atropine (0·01 mg/kg intramuscularly). Oesophagitis was diagnosed in children with friable mucosa together with either erosions or ulcerations, or both.[8] Erythema or granularity, or both, of the mucosa were not considered reliable markers of oesophagitis. Diagnosis of hiatal hernia was established if, during endoscopic visualisation of the gastro-oesophageal junction from below (by upward deflection of the tip of the fibre endoscope in the stomach), gastric folds were observed to slide upward.

Thirty three children, 20 boys and 13 girls aged 2 to 42 months of age (mean, 9 months), met the criteria for gastro-oesophageal reflux with oesophagitis. Thirteen had a different final diagnosis including gastro-oesophageal reflux without oesophagitis (five), cows' milk protein intolerance (three), coeliac disease (two), intestinal malrotation (one), and urinary tract infections (two).

Children with a diagnosis of gastro-oesophageal reflux and oesophagitis were allocated in a randomised fashion to 12 weeks' treatment with either cimetidine syrup (20 mg/kg/day) or liquid magnesium hydroxide and aluminum hydroxide in a dose of 700 mmol (mEq)/1·73 m^2/day, one and three hours after meals, and at bedtime. All children underwent positional treatment (infants remained in an infant chair for the whole day and six inch blocks were put under the head of the bed of children older than 1 year) and received fractionated feeds. In infants, formula milk was thickened by adding cereals or Nestargel (1%). At the end of a 12 week period of intensive treatment the children's condition was evaluated by a careful history and physical examination, pH measurement, and an upper endoscopy. Their condition after treatment was classified on the basis of the presence of remaining symptoms, reflux on pH measurement, and endoscopic features of oesophagitis. Children were regarded as 'cured' if the clinical, pH, and endoscopic parameters became normal; 'improved' if findings in at least one of the three parameters had ameliorated; and 'unchanged' or 'worsened' if there was no improvement or deterioration, respectively. Patients who improved underwent a further month of treatment and were again assessed clinically, by pH measurement and by endoscopy. During the trial, children were seen as outpatients every three weeks to assess symptoms and drug compliance. Parents were instructed to report daily, in a diary, symptoms as well as body weight and food intake. At each examination, haemoglobin, haematocrit, red and white blood cell count, alkaline phosphatase, electrolytes, serum calcium, and phosphorus were evaluated in all children. Creatinine, blood urea nitrogen, transaminase, and α-glutamyltransferase were measured additionally in children on cimetidine treatment. A scoring system was used to evaluate children admitted to the trial (Table 1). The pH measurement,

Table 1 *Scoring system in the evaluation of children with gastro-oesophageal reflux and oesophagitis*

Variables	*Score*
Vomiting, regurgitation (no episodes/wk)	
>5	12
2–5	9
0–1	6
Absent	0
Anorexia	
Severe	4
Moderate	2
Absent	0
Pneumonia, apnoea (no episodes/3 mths)	
>1	15
1	10
<1	0
Anaemia	
Below 1 year of age (haemoglobin g/dl)	
>10	0
9–10	3
7–8·9	6
<7	9
Above 1 year of age (haemoglobin g/dl)	
>11	0
10–11	3
8–9·9	6
<8	9
Weight:height ratio (centiles)	
<5th	6
5–10th	4
>10–<25th	2
25–<50th	1
≥ 50th	0
Endoscopy findings	
Moderate oesophagitis*	6
Severe oesophagitis†	9
pH study (no of episodes of gastro-oesophageal reflux per hour)	
0–1	0
2–4	4
5–6	8
>6	12

*Erythema with friability and exudate.
†Erosions, ulcerations.
In both * and † the score was increased by 3 points in presence of hiatal hernia.

oesophageal manometry, and endoscopy were performed by one of the authors who did not know which treatment patients were being given.

Results

The symptoms and physical findings in 33 children with gastro-oesophageal reflux and oesophagitis are reported in Table 2; either vomiting or regurgitation, or both, and a low body weight were the most frequently encountered. Anorexia, hypochromic anaemia, and haematemesis also occurred. Respiratory complications such as recurrent pneumonia or apnoea were present in 18% of the children studied. Twenty nine children completed the trial (15 on antacid and 14 on cimetidine). Two patients in the cimetidine group were excluded because of poor drug compliance, and two children in the antacid group were excluded because of diarrhoea and subsequent reduced antacid intake. The parameters of gastro-oesophageal reflux of both groups are shown in Table 3; these were comparable statistically. Twelve children had both a body weight and a weight:height ratio below the fifth centile before treatment. In seven (three on cimetidine and four on antacid) both parameters became normal after 12 weeks' treatment. Five children (three on cimetidine and two on antacid) were gaining weight, but their weight:height ratio still remained below the fifth centile. Three of four patients who had a body weight below the fifth centile but a normal weight: height ratio before treatment showed a body weight within normal limits after 12 weeks of treatment (two on cimetidine and one on antacid); the fourth child (on antacid) still had a weight below the fifth centile.

As shown in Table 4, there was a significant reduction in the scores of clinical, pH measurement, and endoscopic findings in both groups. At the end of the 12 week trial, eight patients on antacid and seven on cimetidine were cured, five patients on antacid and six on cimetidine improved and two patients on antacid and one on cimetidine remained unchanged. The latter three patients underwent surgery (Table 5). The basal lower oesophageal sphincter pressure before treatment did not correlate with the total score after treatment (including clinical, pH measurement, and endoscopic scores) in either the cimetidine treated (r:0·25; NS) or antacid treated groups (r:0·32; NS).

Table 2 *Symptoms and signs in 33 children with gastro-oesophageal reflux and oesophagitis (mean age 9 months; range 2 to 42 months)*

	No (%)
Vomiting, regurgitation	31 (94)
Anorexia	9 (27)
Pneumonia, apnoea	6 (18)
Haematemesis	2 (6)
Weight below 5th centile	16 (48)
Weight:height ratio below 5th centile	12 (36)
Anaemia	6 (18)

Table 3 *Clinical, pH, oesophageal manometry, and endoscopic variables before treatment*

	Antacid	*Cimetidine*
No	15	14
Age (months)		
Mean	9·4	8·9
Range	2–42	2–34
Boys	7	10
Girls	8	4
Lower oesophageal sphincter pressure (mmHg), mean (SD)	11·2 (5·8)	10·5 (3·5)
Clinical score,* mean (SD)†	17·30 (3·7)	18·0 (2·9)
pH study score, mean (SD)†	6·45 (3·07)	7·6 (3·4)
Endoscopy score,‡ mean (SD)†	8·2 (2·39)	8·14 (2·17)

*Clinical score included either vomiting or regurgitation, or both; weight failure; anorexia; and respiratory symptoms.
†No statistically significant difference between the two groups of patients ($P > 0.05$).
‡Ten patients were affected by hiatal hernia (6 on antacid and 4 on cimetidine).

Table 5 *Final outcome in 26 patients with gastro-oesophageal reflux and oesophagitis after 12 weeks treatment*

Patient group	*No*	*'Cured' No (%)*	*'Improved' No (%)*	*'Unchanged' or 'worsened'* No (%)*
Antacid treated	15	8 (53·5)	5 (33·3)	2 (13·3)
Cimetidine treated	14	7 (50)	6 (42)	1 (7·15)

*Two patients (1 on antacid and 1 on cimetidine) were affected by hiatal hernia.

Table 4 *Comparison between scores before and after treatment (mean (SD)) for patients treated with antacid or cimetidine*

	Antacid			*Cimetidine*		
	Before treatment	*After treatment*	*Significance**	*Before treatment*	*After treatment*	*Significance**
Clinical score	17·3 (3·7)	3·72 (3·88)	$P<0.05$	18·0 (2·9)	4·01 (3·86)	$P<0.05$
pH study	6·45 (3·07)	0·92 (2·4)	$P<0.001$	7·6 (3·4)	0·61 (2·20)	$P<0.001$
Endoscopy	8·2 (2·39)	3·4 (3·18)	$P<0.01$	8·14 (2·17)	3·21 (3·80)	$P<0.01$

*Student's *t* test for paired samples.

Discussion

Gastro-oesophageal reflux and peptic oesophagitis can be treated by increasing intragastric pH and lower oesophageal sphincter strength, by improving oesophageal acid clearance, and by improving the rate of gastric emptying.[9] Although antacids seem to be useful because of their capacity to neutralise gastric contents and increase lower oesophageal sphincter tone, the latter probably as a result of gastric alkalinisation,[10] their effectiveness in the treatment of gastro-oesophageal reflux and peptic oesophagitis has rarely been studied. In most treatment trials in adults, cimetidine or drugs such as bethanechol or metoclopramide which act on either lower oesophageal sphincter tone or oesophageal peristalsis, or both, have been used,[9] and the level of consumption of antacids has been considered as a measure of the effectiveness of the main treatment. The results of trials in adults using antacids are not conclusive. Behar *et al*[11] did not find any significant effect on the healing of oesophagitis. Thanik *et al*[12] and Saco *et al*[13] found a significant improvement in symptoms and oesophagitis healing rate, probably because of a more frequent administration of larger doses of antacids. More recently, Graham and Patterson[14] failed to observe any significant difference between antacids and placebo in either the relief of symptoms or in the healing rate of oesophagitis.

In contrast with antacids, many trials with cimetidine have been performed in adults. A number of studies showed that cimetidine, although relieving symptoms, did not result in the healing of oesophagitis.[15–18] Other studies have shown a clear cut resolution of symptoms and an improvement in either endoscopic or histological changes in the oesophagus, or both.[19 20] Histamine H_2 receptor antagonists seem to be useful in the management of the reflux disorder, mainly by decreasing gastric acid secretion, but have no effect, however, on oesophageal motility variables.[21]

We performed a trial with cimetidine and large doses of antacids in children with gastro-oesophageal reflux and severe oesophagitis. Oesophagitis was assessed by endoscopy only. Indeed, only endoscopic findings of advanced inflammation (friability, erosions, ulcerations) which correlated well with histological oesophagitis were used in the present study.[22 23] A placebo group was not included since patients had oesophagitis and most of them showed systemic complications such as failure to thrive, anorexia, anaemia, and respiratory symptoms. Apart from either vomiting or regurgitation, or both, the most frequently reported symptoms of gastro-oesophageal reflux in children were respiratory—present in 18% of the patients. Pulmonary complications, considered a common finding in these children, may occur without vomiting or regurgitation and are a frequent indication for surgery in patients in whom medical treatment has failed.[2 24] Sixteen patients showed a weight below the fifth centile and 12 of them a weight:height ratio below the fifth centile. Nowadays gastro-oesophageal reflux in children is regarded as one of the causes of failure to thrive.[1 2] This may be related to a reduced caloric intake because of anorexia or vomiting. The most plausible explanation for the refusal of foods is an increased exposure of the inflammed oesophageal mucosa to acid after eating. In the antacid and cimetidine groups, eight and seven children respectively were cured. Five patients on antacid and six on cimetidine improved. It is worth mentioning that patients who improved recovered completely after a further month of treatment. Three children (two on antacid and one on cimetidine) needed operative treatment: interestingly, two of them had hiatal hernia, a factor known to carry a bad prognosis in gastro-oesophageal reflux.[8] In some of the children who showed failure to thrive before entering the trial, there was a significant increase in body weight at the end of the 12 week follow up period. This is probably due to a decreased frequency of vomiting, resulting in an improved nutritional state. There was a statistically significant reduction in the scores after treatment for clinical, pH measurement, and endoscopic variables in both antacid and cimetidine treated children. A correlation between lower oesophageal sphincter pressure before treatment (normal values 12 mmHg or more) and final total score could not be shown. This is in accordance with the finding that a decreased basal lower oesophageal sphincter pressure is not obligatorily associated with gastro-oesophageal reflux and oesophagitis, implying that other mechanisms play a role in the pathogenesis of reflux disease.[25]

The results of the present trial indicate that medical treatment of gastro-oesophageal reflux and peptic oesophagitis in children is effective in relieving the symptoms of reflux and in promoting healing of the oesophagitis. Antacids administered in high doses, proved to be as effective as cimetidine in healing peptic oesophagitis. These results differ from those in adults in whom healing of peptic oesophagitis was not consistently achieved by medical treatment. This may be explained by the natural course of gastro-oesophageal reflux disease in children.

The natural history of gastro-oesophageal reflux in infants was well described by Carre in 1959.[26] Sixty per cent of these children become asymptoma-

tic at the age of 18 months even without any treatment, five per cent will develop an oesophageal stricture, five per cent will die, and 30% will have persisting symptoms. Therefore, one may reasonably expect a beneficial effect from medical treatment in children. There are good reasons for accepting that in children over the age of 2 years the course of the reflux disease is not much different from that in adults where gastro-oesophageal reflux seems to be a long lasting problem. Infants with sporadic regurgitations may be successfully managed by careful handling, frequent, small feeds, and maintaining an upright position after feeding. Children with moderate symptoms of reflux will benefit from postural manoeuvres and from thickened fractionated feeds. Medical treatment of gastro-oesophageal reflux in children is required in the presence of oesophagitis and systemic symptoms such as respiratory complications, failure to thrive, anaemia, and anorexia.

Better understanding of the pathogenesis of gastro-oesophageal reflux[9 25] may result in more adequate treatment. As basal lower oesophageal pressure does not seem to be correlated with the occurrence of oesophagitis and with the final outcome of treatment, efforts should also be concentrated on such measures as increasing gastric pH and oesophageal and gastric motility. The newly available antisecretory drugs such as H_2 receptor antagonists do not seem to be more effective than antacids in treating reflux in children. The latter, however, in order to be effective, have to be administered in exceedingly high doses, with possible side effects.[27] New drugs acting on gastro-oesophageal motility such as bethanechol (a cholinergic agent)[3 4] and domperidone (a dopamine antagonist)[28] are promising treatments for the future.

Further controlled treatment trials comparing different drugs and including a placebo group are necessary to determine the most effective treatment for children with gastro-oesophageal reflux.

We thank Drs Corazziari and Coremans for their critical reviews of the manuscript.

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Correspondence to Dr S Cucchiara, Clinica Pediatrica, 2^ Facoltà di Medicina, Via S Pansini 5, 80131 Napoli, Italia.

Received 14 May 1984

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