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Effects of cisapride on parameters of oesophageal motility and on the prolonged intraoesophageal pH test in infants with gastro-oesophageal reflux disease

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Abstract

The effect of cisapride, a new gastrointestinal prokinetic drug, on oesophageal motility and acid reflux was studied in 14 children with gastro-oesophageal reflux disease, receiving either placebo or cisapride 0·15 mg/kg intravenously. Cisapride significantly ($p<0·01$) increased the lower oesophageal sphincter pressure (+124%), the amplitude (+84%) and duration (+24%) of oesophageal peristaltic waves, whereas the placebo treatment did not produce any changes. Subsequently, all 14 children underwent 24 hour oesophageal pH-monitoring before and after four weeks of treatment with oral cisapride 0·2 mg/kg tid given in addition to postural therapy and thickened feedings. The 24 hour intraoesophageal pH recordings and symptomatic scores were compared with those of 10 control patients treated only by postural therapy and thickened feedings. When compared with baseline pH data, cisapride significantly reduced the oesophageal acid exposure time, the mean duration of each reflux episode, the duration of the longest reflux episode and the number of long lasting reflux episodes; the number of reflux episodes was not influenced. The effect of cisapride was marked and consistent during fasting and sleep periods. Oesophageal acid exposure was reduced more significantly in patients given cisapride (−61%) than in controls (−24%; $p<0·001$). Symptom improvement was greater after four weeks of cisapride treatment (score reduction: 61%) than after postural and dietary therapy alone (score reduction: 42%; $p<0·01$). No adverse effects occurred. These findings suggest that cisapride is a valuable drug in the management of gastro-oesophageal reflux disease in children.

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Gastro-oesophageal reflux (GOR) disease is one of the commoner problems encountered by paediatricians, potentially causing serious morbidity and even mortality.[1,2] Motility disorders of the upper gastrointestinal tract, such as reduced competence of the lower oesophageal sphincter (LOS), defective oesophageal acid clearance and delayed gastric emptying are important factors in the pathogenesis of the disease.[3] Therefore, drugs that improve the motor function of the upper gastrointestinal tract seem particularly appropriate for patients with GOR disease.

Cisapride (R 51 619, Janssen Pharmaceutica) is a novel 'prokinetic' agent which acts mainly through facilitation of acetylcholine release from the intestinal myenteric plexus.[4] A recent study suggests, however, that cisapride may, in addition, stimulate muscarinic M2 smooth muscle receptors of the stomach.[5] Cisapride has been successfully used in the treatment of clinical conditions that result from a defective intestinal motor coordination, such as GOR, gastroparesis and intestinal pseudo-obstruction.[6-8]

With a view to developing a rationale for the use of cisapride in the therapy of GOR in paediatrics, we investigated, in a double blind fashion, the acute effect of an intravenous dose on oesophageal motility variables in infants with GOR disease. In the same patients, we also evaluated the effects of oral chronic administration of cisapride both on prolonged intraoesophageal pH testing and on GOR symptoms.

Methods

SUBJECTS

Fourteen patients (group A) aged 15·7 (11·5) months (mean (SD)) (range: 2–38 months) were referred to our division over a one year period with symptoms and signs suggestive of GOR (Table I).

Informed consent was obtained from the parents of all infants and the study was approved by the Ethical Committee of our Faculty.

Oesophagitis was documented in seven cases by endoscopy and biopsy. In none of the patients was there any evidence of neurologic, metabolic, infectious, or alimentary disorders. Oesophageal manometry and continuous recording of distal oesophageal pH were obtained in all subjects. Manometry was performed by three water filled polyvinyl tubes (id 0·6 mm) assembled with tetrahydrofuran and set up to measure intraluminal pressure at three points, 2·5 cm apart, through distal side openings oriented at 120°. The recording tubes were infused with distilled water by a low compliance pneumohydraulic system (Arndorfer Med Spec) at a constant rate

TABLE I *Clinical findings in 14 children with gastro-oesophageal reflux (GOR) disease receiving intravenous infusion of cisapride or placebo*

	Cisapride	*Placebo*
Cases (n)	7	7
Mean (SD) age (mo)	13·8 (7·7)	17·5 (14·1)
Range age (mo)	6–14	2–38
Vomiting (and/or regurgitation)	7	7
Apnoea, choking	1	3
Anorexia, irritability	2	3
Oesophagitis	4	3
Weight/height (centile) ≤10th	2	4

of 0·6 ml/min (the pressure rise upon occlusion of the distal side holes was >300 mmHg/s). Each manometric probe was connected to a Beckman ink writing recorder (R 611) (paper speed 2·5 mm/s) through external transducers (Statham P23D). The manometric catheter was passed into the stomach through the nostril in the early morning after a six to eight hour fasting period and was positioned with all orifices in the stomach. Infants were allowed to become restful before the examination was started: this was facilitated both by the small size of the probe and by the administration of cow's milk. In some cases, mild sedation was provided (meperidine 1 mg/kg im). The assembly was withdrawn (0·25 cm at a time) through the gastro-oesophageal high pressure zone. End expiratory lower oesophageal sphincter pressure (LOSP, mmHg) was recorded with the mean intragastric pressure used as zero reference. The mean of three separate pull through determinations was calculated in each patient. After positioning of the distal side hole 1 cm above the upper margin of the LOS, swallows were induced for quantitative assessment of peristalsis by the administration of 2–5 ml of 5% dextrose solution. Only waves preceded by at least 20 seconds of motor silence in the oesophageal body were taken into account. Swallows were recorded by means of cutaneous electrodes (Red Dot 3 M) attached to the suprahyoid region.

Amplitude (mmHg) and duration (s) of oesophageal peristalsis were determined and a mean value was calculated for five peristaltic complexes and for the three side holes above the LOS. Wave amplitude was defined as the difference between the mean oesophageal baseline pressure and the peak of the contraction. The duration of oesophageal contractions was defined as the time from the onset of the major upstroke of the wave to the return of the wave to the baseline. The propagation velocity (cm/s) was calculated by determining the time between the onset of the rapid upstroke of motor waves at the proximal and distal recording sites and dividing it by 5 – that is, the distance between these sites.

After the baseline manometry, each subject received a slow intravenous injection of cisapride 0·15 mg/kg (Janssen Pharmaceutica, Beerse, Belgium), or placebo over a five minute interval. The test drug was diluted to a total volume of 10 ml with 5% dextrose solution. Values of lower oesophageal sphincter pressure and peristalsis variables were then again determined: a slow pull through across the LOS was performed and swallows were elicited 15, 30, 60, and 90 minutes after drug administration. Manometric tracings were coded and read by two independent investigators. On separate days, all subjects underwent 24 hour intraoesophageal pH testing and oesophagoscopy with biopsy. A small flexible electrode (1·5 mm diameter, Ingold) was inserted transnasally. It was standardised against buffer solutions at pH 4 and 7 before and at the end of each recording session: no pH drifts exceeding 0·3 pH unit were accepted. The electrode was positioned with its tip at 87% of the nares-LOS distance as measured by manometry. Gastro-oesophageal reflux was defined as a decrease in the distal oesophageal pH to below 4 for at least 20 seconds, or as the occurrence of an additional decrease of at least 1·0 pH unit during periods of pH less than 4. All patients tolerated the examination well. Children were given the usual daily feeds in a volume determined by their appetite. Oesophageal pH was recorded on a modified computer monitor (Proxima 'ligth', Sensormedics, Italy) and analysed on an IBM personal computer. The following variables were analysed: (1) percentage of time the oesophageal pH was less than 4 (% GOR); (2) number of GOR episodes; (3) number of GOR episodes lasting >5 minutes; (4) mean duration of reflux (total time pH<4 divided by the number of GOR episodes); (5) duration of longest episode of reflux (min).

Analysis of the pH tracings was geared to the entire recording period, the waking and sleep periods, which, together, constitute the entire period, and the postprandial (less than two hours after feeding) and fasting periods (more than two hours after feeding) which, together, also constitute the entire period. Endoscopy was performed in all patients with a paediatric fibrescope (GIF XP10 Olympus) after administration of intravenous diazepam (0·3 mg/kg) and meperidine (1 mg/kg). Two mucosal specimens were taken through the bioptic channel of the endoscope for histological diagnosis of oesophagitis. The latter was classified as mild when 1 to 19 intraepithelial eosinophils and/or 4 to 19 neutrophils per high power field were seen; as moderate when ≥20 eosinophils and/or ≥20 neutrophils per high power field were observed, and as severe if there was also evidence of mucosal ulceration. Endoscopic findings such as oerythema or oedema were not considered reliable indicators of oesophagitis.

The 14 patients were subsequently treated for six weeks with oral cisapride (syrup 1 mg/ml) at a dose of 0·2 mg/kg three times daily before feedings, while postural and dietary measures (prone positioning and thickened feedings) were taken. At the end of the fourth week of therapy, both clinical assessment and 24 hour intraoesophageal pH testing were repeated. On completion of the six week period of treatment, the condition of the patients was assessed by careful history and physical examination. Patients were seen as outpatients every two weeks to assess symptom (Table II) and drug acceptance. Both ambulatory follow up and final clinical examination were performed by a member of our team who was unaware of the pH test and endoscopic results. Laboratory data (blood counts, urinalysis, serum transaminase, alkaline phosphatase, bilirubin, creatinine, urea nitrogen, serum electrolytes) were obtained before and after the six weeks of therapy.

Both pH-monitoring and symptoms assessment were also performed in a second study sample (Group B) consisting of 10 infants (seven boys+three girls) aged between four and 19 months (mean (SD): 10 (4·9) months), with a 24-hour pH-metric diagnosis of GOR and a clinical history of recurrent vomiting and/or regurgitation. Three patients had episodes of choking and/or nocturnal cough and/or recurrent bronchitis, four patients had shown irritability and/or refusal at feeding, and in three cases

TABLE II *Scoring system for the clinical evaluation of children with gastro-oesophageal reflux (GOR) disease*

Symptoms or physical signs	*Evaluation*	*Score*
Vomiting and/or regurgitation or both (episodes/week)	none	0
	1–3	4
	>3<7	8
	≥7	12
Pneumonia or asthma (episodes/month)	none	0
	1	5
	>1	10
Apnoea, choking, nocturnal cough (episodes/week)	none	0
	1–2	5
	>2–5	10
	>5	15
Haematemesis (episodes/month)	none	0
	1–2	5
	>2	10
Irritability, anorexia	mild	2
	moderate	4
	severe	6
Weight/height ratio (centile) >10th<25th	≥50th	0
	≥5th<50th	1
	>10th<25	2
	5th–10th	5
	<5th	10

moderate oesophagitis was documented. These patients were treated for four weeks with postural and dietary measures (upright prone positioning during sleep and for most of the day, and thickening of feedings) and were not given any drugs. After this four week period, they were treated with oral cisapride (0·2 mg/kg three times daily, 15 minutes before meals) for six weeks and were seen as outpatients every two weeks for clinical assessment.

Statistical analysis was performed using non-parametric Signed Rank test. Significance was defined as $p<0·05$. All manometric and pH-values, and symptom scores are given as mean (SD) values.

Results

Seven patients were given an intravenous infusion of cisapride and seven received placebo. The basal lower oesophageal sphincter pressure was 14·47 (8·08) mmHg in patients on cisapride and 13·50 (5·37) mmHg in patients on placebo. Cisapride induced a significant increase in lower oesophageal sphincter pressure throughout the period of manometric examination. Lower oesophageal sphincter pressure had already risen significantly 15 minutes after cisapride administration, reaching a peak value at 60 minutes (32·41 (10·2) mmHg; $p<0·01$; change +124%) and remaining significantly raised throughout the 90 minute recording period (Fig 1). In the placebo group, no change in lower oesophageal sphincter pressure was observed. The basal

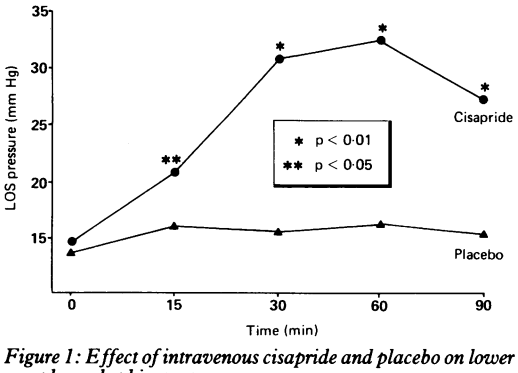

Figure 1: Effect of intravenous cisapride and placebo on lower oesophageal sphincter pressure.

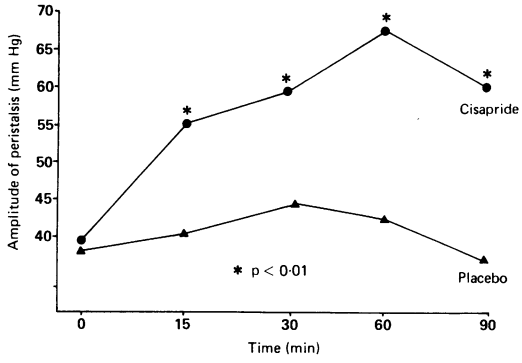

Figure 2: Effect of intravenous cisapride and placebo on amplitude of oesophageal peristalsis.

amplitude of peristalsis was 39·75 (23·74) mmHg in the cisapride patients and 39·02 (16·93) mmHg in the placebo patients. Cisapride induced a significant increase in peristalsis amplitude that was sustained for up to 90 minutes after drug administration, the maximum value occurring at 60 minutes (67·1 (35·77) mmHg; $p<0·01$; change +84% (Fig 2). Peristalsis amplitude did not change after infusion of placebo throughout the 90 minute period of recording. After cisapride there was a significant increase in peristalsis duration (basal value: 2·82 (0·72)) which reached significance from 15 to 90 minutes after drug infusion. The peak duration occurred at 60 minutes (3·51 (1·09); $p<0·01$; change +24%). Persistalsis duration was unchanged following placebo infusion (Fig 3). There was no significant change in peristalsis velocity either after cisapride (basal value: 2·63 (1·37) cm/s) or placebo (basal value: 2·57 (1·47) cm/s) throughout the period of recording.

The results of both basal and four week pH probe studies performed in the 14 patients treated with oral cisapride appear in Table III. There was a significant improvement of the intra-oesophageal pH variables for the total recording period, the fasting period and the waking and sleep periods, whereas only % GOR and duration of the longest reflux episode significantly decreased in the postprandial period. The change in number of GOR episodes did not reach significance in any of the various temporal phases of the pH analysis.

The clinical assessment revealed a significant improvement of the symptom score (baseline: 16·21 (3·72), week 4: 7·57 (3·93), $p<0·001$ with reference to baseline; week 6: 2·64 (2·34),

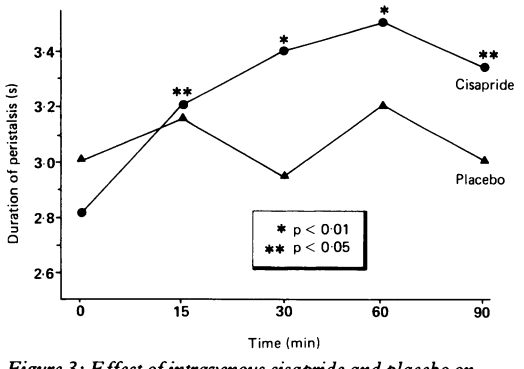

Figure 3: Effect of intravenous cisapride and placebo on duration of oesophageal peristalsis.

TABLE III *Pre and post-treatment 24 hour intraoesophageal pH variables in 14 children treated by oral cisapride*

	GOR (%)	GOR episodes (n)	GOR episodes >5' (n)	Mean duration of GOR (min)	Longest GOR episode
24 Hours					
Pretrial	10·7 (3·4)	43·3 (33·9)	5·8 (2·4)	5·7 (4·9)	33·0 (29·2)
Post-trial	4·0 (1·2)*	28·3 (12·3)‡	2·0 (1·9)*	2·6 (1·9)*	8·9 (9·4)*
<2 Post-prandial hours					
Pretrial	12·2 (7·2)	24·7 (30·5)	2·3 (1·6)	3·9 (3·0)	17·2 (16·7)
Post-trial	4·5 (3·7)*	12·1 (9·4)‡	1·5 (3·4)‡	2·6 (2·5)‡	6·8 (10·1)†
After 2 post-prandial hours					
Pretrial	9·8 (4·8)	18·9 (9·1)	3·5 (1·9)	6·0 (4·9)	24·8 (18·3)
Post-trial	3·7 (2·1)*	16·1 (9·4)‡	1·3 (1·6)†	2·4 (1·3)†	5·3 (2·8)*
Waking period					
Pretrial	9·4 (5·0)	36·6 (35·6)	3·3 (2·2)	2·9 (1·6)	9·8 (6·1)
Post-trial	4·1 (2·5)*	20·5 (9·9)‡	1·2 (1·6)†	2·5 (2·0)‡	6·3 (3·1)†
Sleep period					
Pretrial	13·1 (11·9)	6·8 (5·2)	2·5 (2·5)	9·3 (7·4)	28·9 (31·5)
Post-trial	3·7 (4·3)†	7·9 (9·2)‡	0·8 (1·2)†	3·2 (4·8)†	6·5 (10·2)†

Results are given as mean (SD). Statistical significance: *p<0·01; †p<0·05; ‡ns; in comparison with pretrial values.

TABLE IV *Pre and post-treatment 24 hour intraoesophageal pH variables in 10 children treated by postural therapy and thickened feedings*

	GOR (%)	GOR episodes (n)	GOR episodes >5' (n)	Mean duration of GOR (min)	Longest GOR episode
24 Hours					
Pretrial	9·4 (3·1)	38·2 (22·6)	6·6 (2·9)	7·1 (7·4)	25·9 (10·8)
Post-trial	7·1 (3·3)*	32·1 (14·7)†	4·7 (3·2)*	4·4 (3·7)†	20·4 (16·7)†
<2 Post-prandial hours					
Pretrial	9·0 (4·7)	17·3 (15·2)	2·7 (1·9)	4·2 (1·9)	17·3 (9·2)
Post-trial	9·5 (3·2)†	13·9 (11·8)†	2·3 (2·6)†	4·0 (3·5)†	13·2 (13·3)†
After 2 post-prandial hours					
Pretrial	9·6 (5·7)	20·4 (14·4)	4·0 (2·7)	5·0 (3·7)	20·5 (13·7)
Post-trial	5·6 (3·2)*	18·5 (10·0)†	2·5 (2·0)†	3·5 (3·4)†	12·6 (11·1)†
Waking period					
Pretrial	13·9 (8·8)	30·4 (23·0)	3·5 (3·1)	2·8 (1·7)	13·6 (8·7)
Post-trial	10·5 (8·4)†	24·8 (17·4)†	2·1 (2·7)†	3·5 (4·8)†	7·9 (4·9)*
Sleep period					
Pretrial	6·9 (6·7)	7·9 (5·7)	3·1 (3·5)	8·3 (7·2)	18·7 (16·5)
Post-trial	5·2 (4·6)†	7·4 (6·0)†	2·5 (2·1)†	7·1 (5·4)†	17·3 (16·9)†

Results are given as mean (SD). Statistical significance: *p<0·05; †ns; in comparison with pretrial values.

p<0·001). No adverse effects were observed or reported.

No statistically significant differences were found for the initial symptom score (15·70 (2·26)) and for the initial pH values (Table IV) between the 10 patients who were only treated with postural and dietary measures (group B) and the 14 children treated with oral cisapride (group A). At four weeks, the symptom score in group B was 9·30 (3·74) (p<0·01 *v* baseline value) – that is, a reduction of 42 (16)%. The percentage decrease in score was significantly more marked (p<0·01) in group A, however (61 (14)%). Furthermore, the three patients in group B with respiratory symptoms (one with bronchitis, two with choking and/or nocturnal cough) still had respiratory complaints such as chronic cough and upper airway congestion at the four week clinical assessment. The prolonged oesophageal pH-monitoring in group B (Table IV) showed at four weeks a significant reduction of total and fasting oesophageal acid exposure (% GOR), of the number of GOR episodes of more than five minutes over 24 hours and of the duration of the longest episode of reflux in the waking period, in comparison with the baseline. At the four week pH-monitoring, however, the total time of oesophageal exposure to acid was normal (<2 SD from the mean value in a control population)[9] in only one patient in group B, whereas eight of the 14 patients receiving chronic cisapride showed a normal value for total oesophageal acid exposure. The percentage improvement in 24-hour acid exposure time at four weeks was 61 (19)% in group A and 24 (25)% in group B (p<0·001).

At the end of the six week cisapride treatment after the initial four weeks, the clinical score in group B was 2·60 (2·01) (p<0·01 *v* baseline score).

Discussion

Considerable evidence has recently emerged suggesting that GOR patients have oesophageal and gastric motor abnormalities that contribute to the pathogenesis of GOR disease.[3] Therefore, treatment of GOR disease by motility modulating drugs would be expected to be a rational measure.

A variety of promotility drugs, such as bethanechol (a muscarinic agonist), metoclopramide (a dopamine antagonist with cholinomimetic agonist effects) and domperidone (a benzimidazole derivative with peripheral dopamine antagonist properties) have been used in the treatment of GOR in children as well as in adults.[10,11] There are conflicting reports on the effects of these drugs, both on GOR symptoms and mucosal inflammation.[12-17] It should also be emphasised that these drugs are not devoid of considerable side effects related either to dopamine antagonism or to non-specific cholinergic activity.[18-20]

Our manometric data represent the first controlled study in paediatrics to have evaluated the acute effect of cisapride on parameters of oesophageal motility. Cisapride, which is thought to act selectively on the gut by increased release of acetylcholine from intramural cholinergic nerves, produces a significant increase in LOS basal strength as well as in peristaltic amplitude and duration. These results are consistent with previous studies showing that cholinergic innervation is involved in the regulation of oesophageal motility.[21] *In vivo* studies in animals as well as in man have established that oesophageal peristalsis has a cholinergic component and that the amplitude of peristalsis increases after intramural cholinergic activation.[22,23] In addition, it is generally held that the LOS is innervated by an excitatory cholinergic vagal pathway that can be activated by different stimuli.[24,25] It follows that cisapride offers promise as an effective agent in the treatment of GOR disease.

Gastro-oesophageal reflux occurs whenever there is reduced competence of the gastro-oesophageal barrier.[3] Even though transient phasic LOS relaxation is the most common mechanism of reflux, low basal LOS tone accounts for 20–25% of reflux episodes and becomes a progressively more common mechanism with increasing severity of oesophagitis.[26] It remains to be seen whether cisapride, by increasing the cholinergic tone of the sphincter, decreases the rate and the extent of transient LOS relaxations. Under normal circumstances, once reflux occurs, the oesophagus is efficiently cleared both by peristalsis and by the neutralising effect of saliva.[27] Although the role of saliva is considered critical for the normalisation of the oesophageal pH, defective peristalsis can impair

successful volume clearance and delay acid clearing.[28] In particular, the results of a recent study indicate that amplitude of peristalsis is an important factor in the clearance of refluxed material.[29]

In the present investigation, detailed analysis of pH tracings showed that pH-monitoring variables of acid reflux were significantly improved after four weeks of oral administration of cisapride. Cisapride did not significantly decrease the number of reflux episodes, however, which could indicate that the rate of transient LOS relaxations was not significantly affected by the drug. The effect of cisapride was less prominent in the postfeeding than in the fasting period. In fact, it was significant in the fasting period both while children were awake and asleep. It is possible that gastric distension associated with the meal induces an increase in the frequency and/or the duration of the transient sphincter relaxations, with consequent increased oesophageal acid exposure.[30] It is noteworthy that cisapride also decreased the long lasting GOR episodes and the mean duration of reflux: these variables are commonly believed to be an indirect measure of the clearing ability of the oesophagus and are strongly associated with the occurrence of oesophagitis.[31]

The pH analysis revealed that patients who underwent only positional and dietary therapy showed a decrease in total oesophageal acid exposure (% GOR) four weeks after beginning treatment. This improvement, however, and in particular, the normalisation were significantly less marked than in the cisapride group. It should be also emphasised that administration of cisapride induced a significant decrease in acid exposure during sleep, whereas the latter remained high in patients treated only by positional therapy: indeed, the three patients in the latter group who presented with symptoms involving the respiratory tract were still symptomatic at four week assessment. Even though, as compared with baseline, the four week clinical score was decreased in patients who did not receive any drugs, the score improvement was much more salient in patients treated by cisapride.

Our data indicate that cisapride can be an effective and well tolerated drug for the treatment of symptomatic GOR in paediatrics. Preliminary clinical trials in children have shown that cisapride has significant potential in decreasing symptoms and promoting healing of moderate oesophagitis.[8 32 33] For future therapeutic trials, it would be desirable to include children with severe oesophagitis.

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