A Comparative Study Evaluating The Role of A Prostaglandin (Rioprostil) and H_2 Antagonist (Ranitidine) in Oesophageal Mucosal Protection Against Reflux Induced Oesophagitis

To my patients;

Especially from Dundee, Scotland who made this study possible.

A Comparative Study Evaluating The Role of a Prostaglandin (Rioprostil) and a H_2 Antagonist Ranitidine) in Oesophageal Mucosal Protection against Reflux Induced Oesophagitis

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A thesis submitted for the degree
of Master of Medical Science
University of Natal

June 1997

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Acknowledgements

This thesis was commenced in January 1987 in the Department of Surgery at Ninewells Hospital and Medical School, Dundee, Scotland.

The study was made possible by Professor Lynne Baker, previous Head of Department of General Surgery, University of Natal, Durban and Professor Alfred Cuschieri, Head of the Department of Surgery, University of Dundee, Scotland, whom between themselves arranged for me to work in Dundee. To these gentlemen I am extremely grateful.

I would like to thank Mr. Robert Wood, Senior Lecturer in the Department of Surgery, University of Dundee and Professor Araf Haffejee, Department of Surgery, University of Natal for their encouragement, patience and guidance in supervising the study.

In addition, I received a great deal of help from the following people :

Mr. Craig Eriksen for introducing me to oesophageal function tests.

Professor Kenneth Wormsley, Head of Department of Gastroenterology, University of Dundee for the use of his facilities and allowing me to investigate some of his patients.

Miss Elizabeth Michel and Mr. Angus Reid, Laboratory Technicians, University of Dundee for maintaining pH equipment and storing samples.

Miss Eleanor Gouws, Biostatistician, Medical Research Council, Durban for help with some statistical analysis.

Dr. D. Hopwood, Senior Lecturer, Department of Pathology, University of Dundee for histological analysis of oesophageal biopsies.

Finally, special thanks to Eleanor Conner for typing this thesis.

DECLARATION

I, Anver Dawood Goga, hereby declare that the work on which this thesis is based is original (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another university.

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Presentations and Publications

Does healing of oesophagitis improve oesophageal motor function?

A. Goga, A. Reddy, A. Cuschieri, Departments of Surgery, University of Natal and University of Dundee, Scotland.

South African Medical Journal 1991:80;43.

Presented at 29th congress of South African Gastroenterology Society (SAGES), Bloemfontein 1991.

Prostaglandins compared to H_2 antagonists in the treatment of reflux disease.

A. Goga, A. Reddy, A. Cuschieri, Departments of Surgery, University of Natal and University of Dundee, Scotland.

South African Journal of Surgery 1991:29;171.

Presented at the 20th Annual Meeting of the Surgical Research Society of Southern Africa, Johannesburg 1991.

Prostaglandins and the oesophagus.

A. Goga, Department of Surgery, University of Natal.

Presented at the Faculty Research Day, University of Natal, Durban 1991.

CHAPTER 1
REVIEW OF THE LITERATURE

Reflux oesophagitis can be defined as oesophageal inflammation caused by refluxed material (Dent, 1987).

Gastroesophageal reflux is a daily occurrence in the general population, the symptoms of heartburn and regurgitation being the most common. Approximately 10% of individuals have heartburn and 30% at least once a month (Nebel *et al.*, 1976). Gastroesophageal reflux does not inevitably lead to reflux oesophagitis. In most patients reflux oesophagitis results from excessive exposure of the distal oesophageal mucosa to refluxed gastric contents. This leads to oesophagitis and its attendant complications such as anaemia, stricture, Barretts oesophagus and carcinoma. Oesophageal sensitization and reflux symptoms may well occur without macroscopic evidence of oesophagitis (Dent, 1987).

Asher Winkelstein (1935) was first to introduce the modern concept of reflux oesophagitis. From clinical findings in five patients Winkelstein advanced the novel notion that oesophagitis was caused by the digestive action of gastric juice on the oesophageal mucosa. Prior to this reflux oesophagitis was attributed to causes such as infection, chemical irritants or a secondary effect of cardiospasm, diverticulem or neoplasm. The term reflux oesophagitis, however did not appear in the literature until the 1940's when it was introduced by Allison (1946).

In the 1940's and 1950's it was believed that gastroesophageal reflux was related to anatomical mechanical factors (Allison, 1951). The mere presence of a hiatal hernia became the *sine qua non* of reflux oesophagitis. Reflux symptoms such as heartburn were ascribed directly to hiatal hernia. The rationale of equating hiatal hernia with reflux oesophagitis, a notion still held by some today, collapsed when observers recognized that most patients with hiatal hernia had neither reflux oesophagitis nor reflux symptoms. Further, other patients had reflux

oesophagitis in the absence of a hiatal hernia (Palmer, 1968; Kramer, 1969). Certainly, hiatal hernia and reflux oesophagitis are associated; hiatal hernia predisposing to reflux oesophagitis (Berstad *et al.*, 1986). Stene-Larsen *et al.* (1988) found a coexistance of hiatal hernia and oesophagitis in 68%; Berstad *et al.* (1986) a coexistance of 63%.

The pathogenesis of pathological reflux is multifactorial and has been extensively reviewed in the literature (Janssens & Vantrappen, 1989; Wesdorp, 1986; Crump, 1988; Dodds *et al.*, 1981; Dent, 1987). These factors include -

1. Lower oesophageal sphincter dysfunction (thought to be the major cause, others playing a subsidery role).
2. Abnormal oesophageal clearance.
3. Aggressiveness and volume of refluxate.
4. Defective mucosal resistance.

LOWER OESOPHAGEAL SPHINCTER DYSFUNCTION

The existence of a lower oesophageal sphincter was confirmed over forty years ago by Fyke *et al.* (1956). Instrumentation to measure this sphincter with reasonable accuracy only became available in the 1970's (Dodds *et al.*, 1976). The simplistic concept that the major determinant of reflux oesophagitis was 'lower oesophageal sphincter incompetency' became popularized in the late sixties and seventies (Pope, 1967; Winans *et al.*, 1967; Cohan & Harris, 1970; Haddad, 1979). Low lower oesophageal sphincter pressure values were reported by Cohen & Harris (1971) in patients with reflux symptoms compared to asymptomatic volunteers. Further studies (Dilawari *et al.*, 1973; Krejs, 1974; Miller *et al.*, 1974; Behar *et al.*, 1976; De Meester *et al.*, 1976) invalidated this view and demonstrated that many patients with

symptomatic gastroesophageal reflux had sample values of resting lower oesophageal sphincter pressures that overlapped values from normal subjects.

Early workers (Zyke *et al.*, 1956), not finding a well-defined zone of muscle thickening at the oesophago-gastric junction, as seen in the opossum, explained the lower oesophageal sphincter pressure entirely on the basis of mechanical anatomic factors. These included the mucosal flap at the oesophago-gastric junction, the acute oesophago-gastric angle, the diaphragmatic pinchcock action and the presence of the lower oesophagus in an intra-abdominal location. Current evidence is that these anatomical factors augment the lower oesophageal sphincter pressure rather than account for it (Dent, 1987).

Liebermann-Meffert *et al.* (1979), in a study of fresh human cadavers, have found a zone of thickened muscle using electron microscopy. The maximum thickness is at a point located just above the angle of His. The muscle thickness is asymmetrical and greatest along the greater curvature. The longitudinal fibres are placed in the long axis of the oesophagus. The circular fibres are in the form of rings or clasps. How much this contributes to the sphincter pressure is speculative.

The question as to what then accounts for the lower oesophageal sphincter pressure remains unanswered. Whether it is neurogenic, hormonal or myogenic is not entirely clear (Goyal *et al.*, 1979). The evidence for a neurogenic basis is that atropine causes a substantial decrease of (60-70%) lower oesophageal sphincter pressure in humans, cats and dogs (Dodds *et al.*, 1981). It is postulated that atropine blocks the acetyl choline released by cholinergic vagal nerves. However, in other species, such as opossums atropine does not have any influence on the lower oesophageal sphincter.

As regards the hormonal control, a number of hormones influence the lower oesophageal sphincter pressure when injected intravenously in an excitatory or inhibitory fashion. Gastrin (Lipschitz & Tuch, 1971) and substance P (Mittal *et al.*, 1990) increase the lower oesophageal pressure, whereas cholecystokin, secretin and vasoactive intestinal peptide (Biancani *et al.*, 1984) reduce the lower oesophageal pressure (Lipschitz *et al.*, 1971). It was suggested that gastrin was a major determinant of sphincter pressure but this was subsequently disproved by Sturdevant (1974) in a later study. The current consensus of opinion is that the effects of various hormones on the lower oesophageal sphincter represent pharmacologic rather than physiologic response (Goyal & McGuigan, 1976).

As far as the myogenic contribution to the lower oesophageal sphincter is concerned the recent finding of an 'anatomical' sphincter and how much this contributes, as discussed previously to the pressure is unclear. Certainly in the opossum and monkey where a macroscopically visible sphincter is present the myogenic contribution is important.

The most recent and significant advance in the understanding of the pathophysiology of reflux disease is the demonstration that gastroesophageal reflux occurred in association with transient sphincter relaxations (Dent, 1976). The concurrent measurement of the lower oesophageal sphincter pressure and oesophageal pH was made possible with the Dent sleeve device. For reflux to occur the lower oesophageal sphincter pressure has to be absent. Recent studies (Dent & Holloway, 1988; Dodds & Dent, 1982; Mittal & McCallum, 1988) demonstrate that the proportion of reflux episodes resulting from lower oesophageal sphincter relaxation varies according to the severity of reflux disease. In healthy volunteers reflux occurs almost exclusively during lower oesophageal relaxation, whereas in patients with erosive or ulcerative oesophagitis, two-thirds of reflux episodes occur by this mechanism

(Holloway & Dent, 1990). These findings suggest that it is the defective control of the lower oesophageal sphincter pressure rather than actual basal pressure leading to reflux disease.

The nature, control and underlying mechanisms of transient lower oesophageal sphincter relaxations are incompletely understood. The control is best explained by neural means. Observations that support this view are that cervical blockade in dogs induces complete suppression of transient lower oesophageal sphincter relaxation in dogs (Martin *et al.*, 1986) and that in patients with achalasia transient lower oesophageal sphincter relaxations are absent (Holloway *et al.*, 1989).

Gastric distension has been shown to be a potent stimulus for provoking transient lower oesophageal sphincter relaxations. Studies have established that these relaxations are a normal physiologic response (Wyman *et al.*, 1984; Holloway *et al.*, 1989). It is thought that the stimulation of mechanoreceptors in the gastric wall result in triggering of lower oesophageal sphincter relaxation. The site of these mechanoreceptors is thought to be mainly in the cardia as limiting the distensibility of the gastric cardia by banding in dogs abolishes this reflex (Strombeck *et al.*, 1989).

Supine posture and sleep have been demonstrated to suppress transient lower oesophageal sphincter relaxations (Dent *et al.*, 1980; Wyman *et al.*, 1984). The mechanisms of this suppression is unknown. It is proposed that sensory mechanisms are present at the gastric cardia.

Unfortunately little is known about the control of transient lower oesophageal sphincter relaxation in patients with reflux disease and more investigation is needed. Mittal &

McCallum (1988) in their study suggests that the rates of transient lower oesophageal sphincter relaxations are similar in healthy subjects and in those patients with reflux disease but that the transient lower oesophageal sphincter relaxation in patients are more likely to be accompanied by reflux.

ABNORMAL OESOPHAGEAL CLEARANCE

Prolongation of oesophageal acid clearance among patients with oesophagitis was first demonstrated by Booth *et al.* (1968). In this test he infused 15 ml of 0.1 N HCL (pH 1.2) into the proximal oesophagus of a supine subject and monitored the intra-oesophageal pH with an electrode positioned 5 cm above the lower oesophageal sphincter. The time taken from the instillation of the acid until the pH recovers to 4 is the acid clearance time. The subject is instructed to swallow at 30 second intervals. Similarly in 24 hour distal oesophageal pH recordings of 100 patients with reflux disease De Meester (1976) reported that the mean acid clearance time was markedly prolonged compared with the values of 15 controls. Subsequent studies using larger numbers of patients (Stanciu & Bennet, 1974; Johnson, 1980) showed that not all patients with reflux had prolonged acid clearance times; In Stanciu's study only half had prolonged acid clearance. Recently, Richter *et al.* (1987) using concurrent radionuclide imaging and oesophageal manometry found peristaltic dysfunction in half of patients with severe oesophagitis. This figure was also confirmed by a study of 177 patients by Kahrilas *et al.* (1986). Kahrilas & Dodds (1988) also showed that peristaltic dysfunction lead to prolonged acid clearance.

The question as to whether reflux oesophagitis is primarily a motility disorder or whether the motility disturbance is secondary to the oesophagitis has not been answered clearly and remains controversial.

Animal studies indicate that oesophagitis can cause lower oesophageal sphincter pressures and peristaltic pressures to decrease. Studies in cats (Eastwood *et al.*, 1975) and baboons (Sinar *et al.*, 1980) have shown progressive decreases in lower oesophageal sphincter pressure and distal oesophageal peristaltic amplitude following acid exposure.

In man, improvement in peristaltic function following treatment of the oesophagitis would favour that the motility disturbance is secondary to the oesophagitis. Some reports in the literature show improvement in peristaltic function following treatment (Marshall & Gerhardt, 1982; Gill *et al.*, 1986) but the majority of studies (Behar *et al.*, 1975; Eckhardt, 1988; Baldi *et al.*, 1988) show no change following healing. Further studies with a greater number of patients and over a longer period of time are needed to elucidate the problem.

AGGRESSIVENESS AND VOLUME OF REFLUXATE

The composition and amount of material refluxed into the oesophagus is an important factor in determining the development and severity of reflux oesophagitis.

Evidence from recent studies suggests that the frequency of gastroesophageal reflux is related to gastric volume. A direct correlation has been shown between gastric secretary volume and reflux frequency (De Meester *et al.*, 1981). The amount of reflux increases significantly after a meal in both the physiological state and in oesophagitis patients (De Moraes-filtro & Bittarello, 1974). The tendency for gastroesophageal reflux has been shown to increase with incremental increases in gastric volume (Ahtaridis *et al.*, 1981).

Although traditional therapy implies that gastroesophageal reflux and oesophagitis might be due to abnormal acid secretion, support for this concept is not found in the literature. A number of reports have evaluated acid secretion in groups of patients with a variety of acid/peptic disorders and have shown that reflux oesophagitis is not associated with increased gastric acid secretion. In 1967, Abernethy reported that patients with peptic oesophagitis had normal or low augmented histamine responses. Similarly, Silber (1969) reported there was no correlation between maximal acid secretion and heartburn in a group of patients with hiatal hernia. Stanciu (1975) further developed this concept in a study showing no association between gastric acid secretion and degree of oesophagitis. In addition he showed there was no association between maximal acid output and oesophageal acid exposure times at pH less than 5, 4 or 3 in these patients. A positive association was shown between the severity of oesophagitis and duration of osophageal acid exposure.

Despite that patients with oesophagitis do not have gastric hypersecretion acid, and pepsin are aggressive factors in the gastric pool. Experimentally, it has been shown that gastric acid alone, in levels normally present in the stomach, can cause oesophagitis (Goldberg *et al.*, 1969). Further reports of a high incidence of oesophagitis in patients with the Zollinger-Ellison Syndrome emphasizes the destructive potential of gastric acid in gastroesophageal reflux disease (Richter *et al.*, 1981). Acid actuates pepsin and the combination causes even more severe oesophageal mucosal damage than acid alone, suggesting that pepsin is probably the most aggressive fluid in cases of acid-related reflux (Goldberg *et al.*, 1969; Harmon *et al.*, 1981).

Attention has been paid to the possibility that patients with reflux disease have unusually aggressive gastric juice because of the presence of high concentrations of bile acids in the

refluxate. Early studies (Kaye & Showalter, 1974; Orlando & Bozymski, 1973) have demonstrated increased duodenogastric reflux in some patients with reflux oesophagitis. Bile has been shown experimentally to increase the development of oesophagitis substantially when added to gastric acid (Gillison *et al.*, 1972; Harmon *et al.*, 1981) by increasing the permeability of the mucosa to hydrogen ions (Safaei-Shirazi *et al.*, 1975). Alkaline reflux oesophagitis is commonly recognised in patients having a gastrectomy and may also occur in patients with an intact gastrointestinal tract (Pelligrini *et al.*, 1978).

Recently Mittal *et al.* (1987) found no evidence to support the view that exposure of the oesphageal mucosa to bile acids was excessive in reflux disease. In both healthy control subjects and in patients with reflux disease analysis of the refluxed material following a standardized meal showed no evidence of significant exposure of the oesophagus to bile acids.

MUCOSAL RESISTANCE

The mucosa provides an effective barrier against gastric acid by a number of mechanisms. It is a multilayered non-keratinized epithelium which is 25-30 cells thick. In these cells and between them are large amounts of mucopolysaccharides (Hopwood *et al.*, 1977). The cells further have a high turnover rate of six days (Descher & Lipkin, 1971) and 'tight' junctions with selective permeability have been demonstrated between them (Lacy *et al.*, 1989). These junctions effectively retard hydrogen ion penetration. Orlando *et al.* (1984) has shown that if hydrogen ion is present in the lumen for a significant period at a sufficient concentration it is capable of penetrating through these tight junctions.

The role of endogenous mediators of mucosal protection, although well worked out in the stomach, is unclear in the oesophagus. Of note is that increased levels of prostaglandins have been found in oesophagitis (Alber *et al.*, 1988).

Increased mucosal blood flow in response to luminal hydrogen ion thereby maintaining mucosal integrity has been well demonstrated in the stomach and duodenum (Hawkey *et al.*, 1985; Hirst, 1989). Hollwarth *et al.* (1986) demonstrated increased mucosal blood flow over the lower oesophageal sphincter and in the muscle layer in response to luminal acid perfusion. Bass *et al.* (1984) demonstrated increased mucosal blood flow in response to bile acids or trypsin at neutral pH. It has been suggested that prostaglandins may have a role in regulating mucosal blood low (Goldstein, 1990).

If the exposure to refluxed gastric juice is not excessive increased cellular turnover of oesophageal epithelium keeps pace with increased desquamation, thereby preventing overt oesophagitis. Patients with reflux symptoms may have a normal appearing mucosa on endoscopy but on biopsy show increased thickness of the basal cell layer and prominent papillae without ulceration or inflammatory infiltrate (Ismail-Beigi *et al.*, 1970; Johnson *et al.*, 1978). These histologic changes suggest increased cellular proliferation. Whether this proliferative response will be altered by prostaglandins is not known. Following fundoplication basal cell proliferation has been shown to revert to normal (Johnson *et al.*, 1978).

THE PROSTAGLANDINS

Prostaglandins are acidic lipids with marked biological activities. They are widely distributed in all body tissue including the gastrointestinal tract. All prostaglandins can be considered to be analogues of prostanoic acid. The major precursor of prostaglandins is arachidonic acid, a

fatty acid found in the diet (mainly in meat). Arachidonic acid is transported in blood bound to albumin and then incorporated into cell membrane phospholipids (Sewell, 1985). Arachidonic acid is then converted into its metabolites via prostaglandin synthetase. Drugs which modify arachidonic acid metabolism, eg. aspirin and non-steroidal anti-inflammatory drugs inhibit prostaglandin synthase and thus act to decrease prostaglandin synthesis.

Prostaglandins fall into six main classes, A through F, which are distinguished by constituents of the cyclopentone ring. Prostaglandins of the E and F series are most abundant in body tissues and are called 'primary prostaglandins'. Prostaglandins A, B and C are derivates of E and are therefore secondary prostaglandins.

Prostaglandins exert a very wide spectrum of actions. It is evident that there is no single prostaglandin receptor and different prostaglandins show different activities (Sardle, 1985). The prostaglandins are stable in blood but are degraded and inactivated by tissue bound enzymes. Their major actions are not as distant hormones but as local mediators and modulators (Vane, 1969). The receptor for prostaglandins in many tissues is thought to be related to adenyl cyclase as in many systems prostaglandin effects are thought to be mediated by an increase in cyclic AMP (Hittelman & Buthcher, 1973). Prostaglandin receptors have been discovered in the lower oesophageal sphincter (Goyal *et al.*, 1978). Prostaglandin E1 when administered intravenously causes a dose dependent fall in lower oesophageal sphincter pressure. This inhibitory effect is not antagonised by atropine, vagotomy, alpha or beta adrenergic blocking drugs. These studies (Goyal & Rattan, 1973) suggest that the effect of prostaglandin E1 may be a direct effect on the muscle. Administration of prostaglandin E1 locally in the arterial supply of the lower oesophageal sphincter also causes a fall in the sphincter pressure. The effect of prostaglandin E2 is similar to that of E1 and these two agents

appear to be equivalent in their effects on the lower oesophageal sphincter. Prostaglandin A2 also inhibits the lower oesophageal sphincter but is not as potent as prostaglandin E2 (Goyal & Rattan, 1973). The inhibitory effect of prostaglandin E2 has been shown in healthy subjects and in patients with achalasia (Mukhopadhyay *et* al, 1975). Prostaglandin E2 has been reported to inhibit gastrin stimulated lower oesophageal contraction (Dilawari *et al.*, 1975). Unlike the action of E2, prostaglandin F2 causes contraction of the lower oesophageal sphincter in patients with reflux disease (Dilawari *et al.*, 1975).

Prostaglandins appear to be useful in the treatment of reflux oesophagitis; the reasons being four-fold. They are reported to be antisecretory, cytoprotective, accelerate gastric emptying and have no inhibitory effects on oesophageal motility.

As regarding the reduction of gastric acid secretion this effect was shown in rats in 1967 using locally administered prostaglandin E and A (Robert *et al.*, 1979). Early attempts to transfer this observation to man failed because a lack of oral activity, side effects, short duration of action and temperature instability of the drug. The majority of these problems were overcome by the formation of synthetic prostaglandin analogues. Prostaglandin E1 and E2 analogues have been demonstrated to inhibit gastric acid secretion provoked by histamine (Wilson *et al.*, 1975), pentagastrin (Robert *et al.*, 1974) and a meal stimulus acid secretion by 44% (Demol & Wingender, 1985). The mode of action of prostaglandins in reducing gastric acid secretion is not clear. Prostaglandins do not bind to H_2 receptors or exhibit anticholinergic properties; there is an unconfirmed possibility of a prostaglandin receptor on the parietal cells (Deakin & Colin-Jones, 1985).

The 'cytoprotective' effects of prostaglandins have been extensively studied in the stomach. This term was coined by Robert in collaboration with Jacobson in 1979 to describe the mucosal protection phenomenon displayed by prostaglandins.

Mucus secretion together with bicarbonate ion secretion have a buffering effect to gastric acid and pepsin. The stimulatory effect of prostaglandins on gastric mucus secretion in humans was first demonstrated in 1978. In an experiment conducted in healthy volunteers intragastric instillation of a prostaglandin E analogue resulted in dose-dependant increases in mucus secretion (Domschke *et al.*, 1978). The contribution of prostaglandins to bicarbonate ion secretion has also been documented in animals and humans. In healthy volunteers intragastric instillation of PGE2 and PGE2 analogue was shown to enhance the secretion of bicarbonate ions (Johansson *et al.*, 1983).

Other 'cytoprotective' effects include increasing mucosal blood flow and improving mucosal regenerative capacity. Infusion of PGE1 and PGE2 into the gastric artery in dogs resulted in significant and dose dependent increases in gastric mucosal blood flow (Gherkins *et al.*, 1978). In another study the effect of PGE1 analogue on mucosal blood flow in rats was investigated. Administration of PGE1 analogue during pentagastrin stimulation significantly reduced acid secretion while maintaining increase in mucosal blood flow (Leung *et al.*, 1986). Sato (1987) and co-workers using organ reflectance spectrophotometry to measure blood volume demonstrated that prostaglandin E1 analogue increased blood volume in the human stomach.

Tarnawski and co-workers (1985) showed that in animals with alcohol induced damage to mucosa pre-treatment with prostaglandins resulted in a more rapid restitution of the epithelium

compared to controls. Using electron microscopy this finding was confirmed by Liss *et al.* (1986).

The effects of prostaglandin E1 (Rioprostil) on gastric emptying was studied by Penston *et al.* (1986). It was found to significantly increase the rate of gastric emptying.

A REVIEW OF THE CURRENT MANAGEMENT OF REFLUX OESOPHAGITIS

The therapeutic approach to patients with reflux oesophagitis is three-fold and consists of conservative non-drug measures, drug therapy and surgery. The treatment objectives are to reduce reflux, to neutralize refluxed material, to restore lower oesophageal sphincter pressure and to improve oesophageal clearing.

Non-drug measures include elevating the head of the bed, avoiding tight fitting garments, weight loss in obese individuals, eating of small meals and the cessation of smoking. Drugs that decrease the lower oesophageal sphincter pressure (anticholinergics, calcium channel blockers, theophylline, diazepam, opiates) must be avoided (Tytgat, 1989).

Present drug therapy of reflux oesophagitis is not yet ideal. The drugs used can be divided into the prokinetic agents which enhance gastric motility, mucosa coating agents and drugs which neutralise or suppress gastric acid. The earliest prokinetic agent to be used was Bethanechol, a cholinergic agent which increases lower oesophageal pressure and enhances oesophageal clearing. Thanik & Chey (1982) found Bethanechol to be as effective as cimetidine. However, because of this drugs cholinergic effects (abdominal cramps, urinary frequency, sweating and increased salivation) it is seldom prescribed. Metoclopramide, another prokinetic agent, is a dopamine antagonist that enhances gastric emptying and increases the

amplitude of oesophageal contractions. It also increases the lower oesophageal sphincter pressure. A review of studies using metoclopramide for reflux oesophagitis demonstrates symptom improvement in some (McCallum *et al.*, 1977; Bright-Asare *et al.*, 1980) but inferior efficacy compared to cimetidine or ranitidine (Guslandi *et al.*, 1983; Bright-Asare *et al.*, 1980). An elevated lower oesophageal sphincter pressure was not demonstrated in these studies. Central nervous system effects (fatigue, anxiety, confusion, hallucinations) occurred in up to 30% of patients on metoclopramide. Cisapride is the most recent addition to the prokinetic class of anti-reflux agents. Cisapride elevates lower oesophageal sphincter pressure and increases oesophageal and gastric peristaltic contractions by stimulation of the myenteric plexus (Rode *et al.*, 1987). Cisapride has been found to be markedly more effective than placebo and as effective as ranitidine in reflux disease (Lepoutre *et al.*, 1986; Janisch *et al.*, 1987; Huettemann *et al.*, 1986). When cisapride is combined with H_2 receptor antagonists the clinical response is improved (Galniche *et al.*, 1987, Wienbeck *et al.*, 1986).

Sucralfate, a mucosa coating drug has been found to be superior to placebo and at least as effective as alginic acid (Laitmen *et al.*, 1985). It is a topically active aluminium hydroxide salt that binds to denuded tissue and forms a barrier to bile acid and pepsin. The drug is well tolerated and some studies (Simon *et al.*, 1987) have found sucralfate to be as effective as ranitidine. Alginates also act as a mechanical barrier against acidic/peptic reflux. They are usually combined with an antacid and are available commercially (Gaviscon). Most studies (Chevrel, 1980; Stanciu, 1974) demonstrate better symptom relief than antacids. Endoscopic healing rates were no different from antacid therapy.

Although antacids are the most commonly used agents for treating heartburn evidence of their efficacy is lacking. They have a short duration of action, lack any effect on nocturnal acid

secretion and have the possibility of rebound acid secretion. High dose antacid therapy was compared with placebo and H_2 antagonist therapy in three comparative studies (Furman *et al.*, 1982; Graham *et al.*, 1983; Grove *et al.*, 1985). Endoscopic and symptomatic improvement on antacid therapy was lacking in these studies.

H_2 antagonists are the present 'gold standard' of treatment of reflux oesophagitis. This 'gold standard' has an overall 63% endoscopic and symptomatic healing rate compared to placebo of 36% (Tytgat, 1989). Treatment of reflux oesophagitis with the H_2 antagonists is based on their ability to reduce gastric pH and to reduce nocturnal acid secretion during periods of recumbency. H_2 receptor antagonists neither increase lower oesophageal sphincter pressure or improve oesophageal or gastric clearance (Tytgat & Nico, 1987). Few side effects have been reported with the widespread and sometimes prolonged use of the H_2 blockers. Cimetidine has been associated with mild elevations of serum transaminase without other evidence of liver dysfunction; other adverse effects include small increases in serum creatinine, a wide variety of central nervous system symptoms, including confusion and agitation; and gynecomastia and sexual dysfunction. Ranitidine shares some of the common side effects with cimetidine but has fewer drug interactions. There are fewer reports of central nervous system symptoms with ranitidine and no gynaecomastia or sexual dysfunction has been reported (Grove *et* al., 1988). In comparing cimetidine to ranitidine in the treatment of reflux disease the results of treatment appear to be indistinguishable (Kimmig, 1984). A drawback of H_2 antagonist therapy is that prophylactic treatment is very much less effective than comparable therapy in duodenal ulcer disease (Sherbaniuk *et al.*, 1984).

Omeprazole is a substituted benzimidazole which inhibits the K^+/H^+ transporting ATPase in the parietal cells and thereby results in almost complete prolonged suppression of basal and

stimulated acid secretion (Lind *et al.*, 1986). Results with treatment using Omeprazole are impressive and superior to the H_2 antagonists. Hetzel *et al.* (1986) found an 81% endoscopic healing rate and Dammann (1986) 85% compared to 67% using ranitidine. Side effects were rare, the most common being diarrhoea, nausea, dizziness, weakness and headaches. The main concern with the use of omeprazole is the profound acid suppression produced. The potential effects of this are bacterial overgrowth, elevated serum gastrin levels and hypertrophy of gastric mucosal enterochromaffin-like cells (Friedman, 1987; Warmsley, 1987). The potential carcinogenic risk with long-term use of omeprazole is a lingering concern (Stem *et al.*, 1989).

As each of the therapies for reflux oesophagitis address each component of this multifactorial disorder it is logical to assume that combination therapy would prove to be superior. Overall this has been disappointing. Studies using cimetidine and metoclopramide (Temple *et al.*, 1983), ranitidine and domperidone (Masci *et al.*, 1985), ranitidine and cisapride (Wienbeck *et al.*, 1986) failed to show any significant improvement compared to monocomponent therapy alone.

The final treatment option for reflux oesophagitis is surgical intervention. About 5-10% of patients with gastroesophageal reflux will undergo anti-reflux surgery, either because of medical treatment failure or complications such as stricture, major bleeding, pulmonary aspiration or Barretts oesophagus (Wesdorp, 1986). In the past the most common surgical repair was Allison's procedure, but this has been replaced by the complete fundoplication of Nissen, the posterior gastropexy of Hill and the transthoracic anterior fundoplication of Belsey. The operative mortality ranges from 0.2 to 1.6% (Wesdorp, 1986). Complications are infrequent and include oesophageal perforation, vagal nerve injury, transient dysphagia and the inability to belch or vomit. The effectiveness of anti-reflux surgery has been encouraging

with a success rate of 80-90% (Wesdorp, 1982). However, it has been reported that 25-30% of patients have recurrence of symptoms within six years following surgery (Brand, 1979).

CHAPTER 2
PATIENTS AND METHODS

The role of prostaglandins in patients with reflux oesophagitis was carefully assessed by symptom change, endoscopy, histology, manometry, radionucleide transit studies and 24 hour pH monitoring.

Out-patients aged 18 years or over presenting with symptoms of gastro-oesophageal reflux disease and with endoscopic or histological peptic oesophagitis were studied. The patient's informed consent was obtained in each case. The exclusion criteria were; treatment with H_2-receptor blockers, anticholinergics, sucralfate, bismuth compounds or carbonexolone at the time of diagnosis; concomitant gastric or duodenal ulcer; presence of oesophageal stenosis; previous gastric surgery except for simple closure of perforated ulcer; pregnancy or lactation; concomitant treatment with corticosteroids, anti-inflammatory analgesics or antineoplastic agents; concomitant disease likely to complicate the evaluation of prostaglandins on the oesophagus; and clinically relevant abnormalities in pre-assessment laboratory screening values (blood count, urea, electrolytes, bilirubin, albumin, liver enzymes, blood glucose and urinary metabolites.

Prior to entry in the study a detailed clinical history with particular reference to symptoms of gastro-oesophageal reflux and a complete physical examination were undertaken. Symptoms of gastro-oesophageal reflux were assessed using De Meester's clinical score as described below:

	HEARTBURN	
None	0	No heartburn
Minimal	1	Occasional episodes
Moderate	2	Reason for medical visit
Severe	3	Interference with daily activity
	REGURGITATION	
None	0	No regurgitation
Minimal	1	Occasional episodes
Moderate	2	Predictable on position or straining
Severe	3	Episodes of pulmonary aspiration
	DYSPHAGIA	
None	0	No dysphagea
Minimal	1	Occasional episodes
Moderate	2	Requires liquids to clear
Severe	3	Episodes of oesophageal obstruction

(De Meester, Wang *et al.* (1980)

The score for each of these symptoms is added up to give an overall figure for the symptomatic assessment of oesophagitis.

Oesophago-gastro-duodenoscopy was carried out by the author and the severity of the mucosal damage was coded as normal, minimal, moderate and severe according to Frierson's criteria (1990):

0	Normal
1	Minimal oesophagitis. Discrete scattered areas of erythema and/or superficial erosions.
2	Moderate oesophagitis. Confluent areas of erythema, deeper erosions with or without mild oedema involving most of the circumference.
3	Severe oesophagitis. Raw mucosa often with spontaneous bleeding and ulceration with or without severe oedema (cobblestone appearance).

Multiple biopsies were taken from affected areas including one biopsy from the area within 5 cm of the oesophago-gastric junction. Histological grading was carried out in conjunction with a single pathologist and graded according to severity:

0	Normal oesophageal mucosa.
1	Minimal/mild inflammation. Changes in squamous epithelium with increased thickness of basal layer, nuclear proliferation and elongation of papillae ± mild increase in inflammatory cells in the lamina propria.
2	Moderate inflammation. Moderately heavy infiltration of inflammatory cells within lamina propria together with the epithelial changes described in Grade I.
3	Severe inflammation. Massive and extensive inflammatory cell infiltrate of lamina propria ± mucosa ulceration.

Oesophageal manometry was performed by the author prior and after a twelve week course of treatment. A triple lumen nasogastric catheter (Portex, London, UK) (Illustration 2.1) was used. It has three radially spaced apertures at 5 cm intervals from its tip, and was continually perfused by a low compliance Arndorfer pneumohydraulic infusion system (Arndorfer Medical Specialities Inc., Wisconsin, USA) (Illustration 2.2). Three transducers connected the

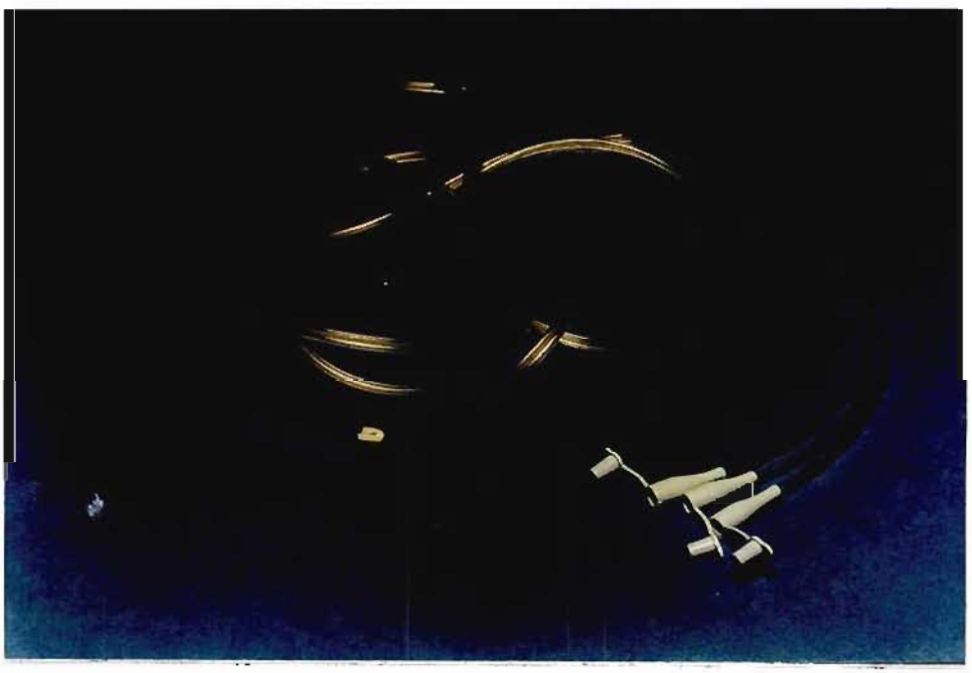


ILLUSTRATION 2.1 Triple lumen nasogastric catheter.

ILLUSTRATION 2.2 Arndorfer pneumohydraulic infusion system.

Arndorfer to a multichannel recorder (Hewlett-Packard, model 7758A, Workingham, Berkshire, UK) (Illustration 2.3) and oesophageal pressure tracings were made on a polygraph. The slow station pull-through technique (Welsh & Drake, 1980) was used to record the characteristics (length, pressure, response to swallowing) of the high pressure zone (lower oesophageal sphincter) and motility of the oesophageal body in response to several dry and wet swallows. Analysis of the manometric tracings included high pressure zone pressure, propagated wave amplitude and durations, and the presence of tertiary non-propagated contractions.

Oesophageal transit was assessed by the oesophageal Egg Test, a test developed by the Departments of Surgery and Nuclear Medicine, Ninewells Hospital, Dundee. The test requires the patient to chew then swallow a 10 ml bolus of poached egg white that has been labelled with 15-20 MBq of technetium sodium pertechnetate. The test is performed in the erect posture and the patient swallows every 20 seconds (Illustration 2.4). Serial one second frames are taken by a scintillation camera for a total of four minutes and the data is stored in an on-line computer (Illustration 2.5).

The series of dynamic frames are compressed into a parametric 'maximum count image'. This single image is created by the computer stepping through serial frames and replacing the count in the same pixel of the next frame only if the value in the second pixel was greater. This image was used to define the body of the oesopahgus using the cricoid and the gastro-oesophageal junction as landmarks. The body of the oesophagus is divided into three equal parts for further analysis.

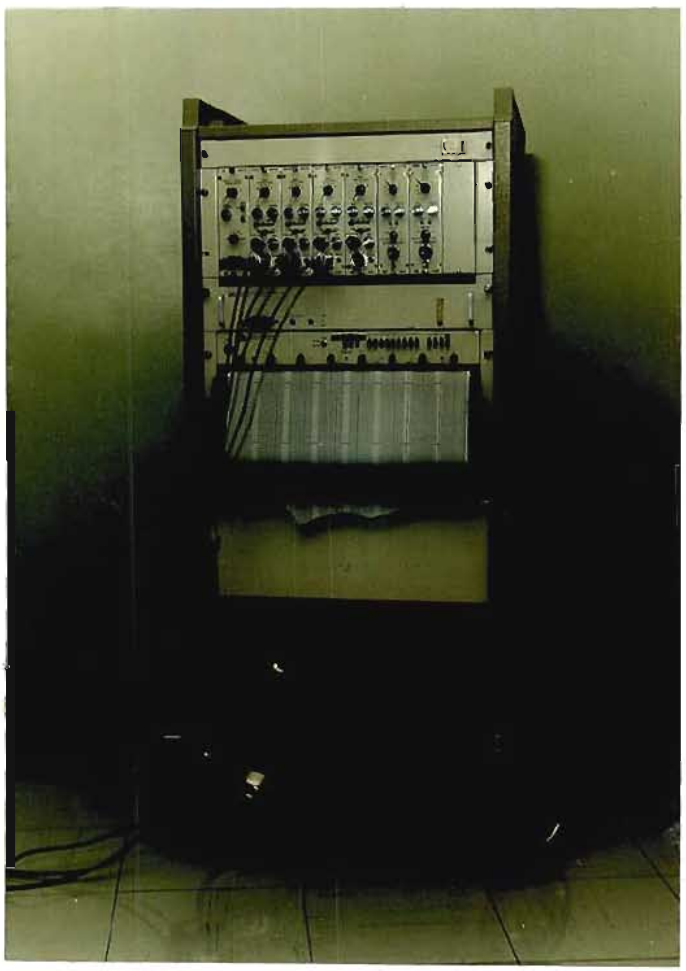


ILLUSTRATION 2.3 Hewlett-Packard multichanel recorder model 7758A.

ILLUSTRATION 2.4 Oesophageal egg test: Scintillation camera.

ILLUSTRATION 2.5 Oesophageal egg test: Condensed computer generated image.

Activity versus time curves, quantifying the passage of the labelled egg white through the entire oesophagus were then generated (Figure 2.1). Transit time was defined as the time from entry of activity until the time >90 percent of the activity had cleared. In addition the region of the oropharynx was also evaluated to ensure that the bolus was swallowed entirely during the initial swallow. To aid interpretation a condensed image was also generated.

To create this computer generated image each consecutive frame of the dynamic study was added side-by-side using a row summation technique. Thus a single view parametrically describing the entire dynamic sequence was generated (Figure 2.2). This condensed image with time on the horizontal axis and the vertical axis representing spatial arrangement of the labelled egg white in the oesophagus and stomach was useful in assessing the pattern of the radionuclide bolus through the oesophagus.

Oesophageal pH monitoring was performed on all patients at the beginning and end of the study. This investigation was pioneered by Rovelstad (1952). He used glass pH electrodes to measure gastric and duodenal pH *in vivo*. Soon after, this technique was applied by Tuttle & Grossman (1958) and Weber & Gregg (1959) in the study of reflux oesophagitis. Little progress was made in the intervening years and it was Johnson & De Meester in North America and Stanciu & Bennet in Britain who were responsible for the rise in popularity and increased sensitivity in prolonged oesophageal pH monitoring. Vitale *et al.* (1984) working at Ninewells Hospital in Dundee developed a computerised 24 hour oesophageal pH monitoring system and this system was used in this study.

Oesophageal pH was measured using a radiotelemetry pill (Medici Developments Ltd, London) (Illustration 2.6) which was suspended 5 cm above the manometrically determined

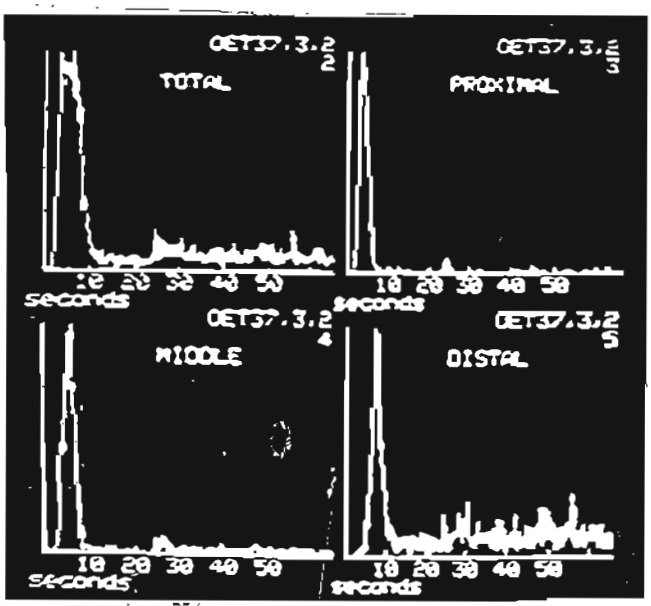


FIGURE 2.1 Activity vs. Time labelled egg white.

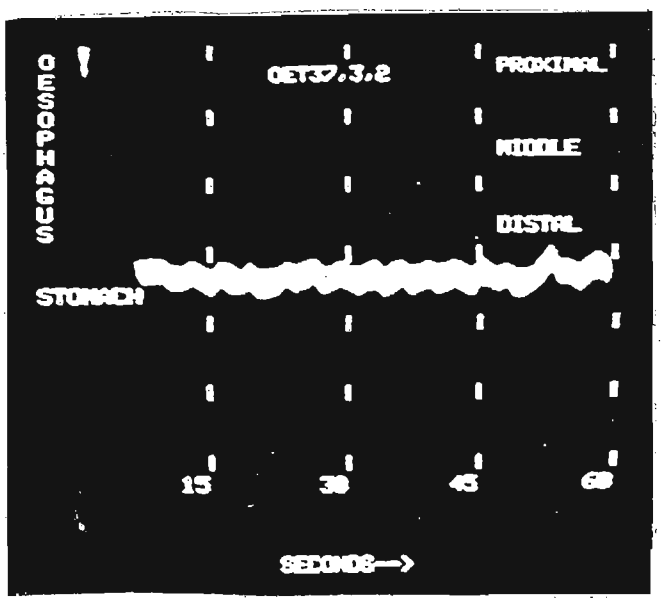


FIGURE 2.2 Condensed image of labelled egg white.

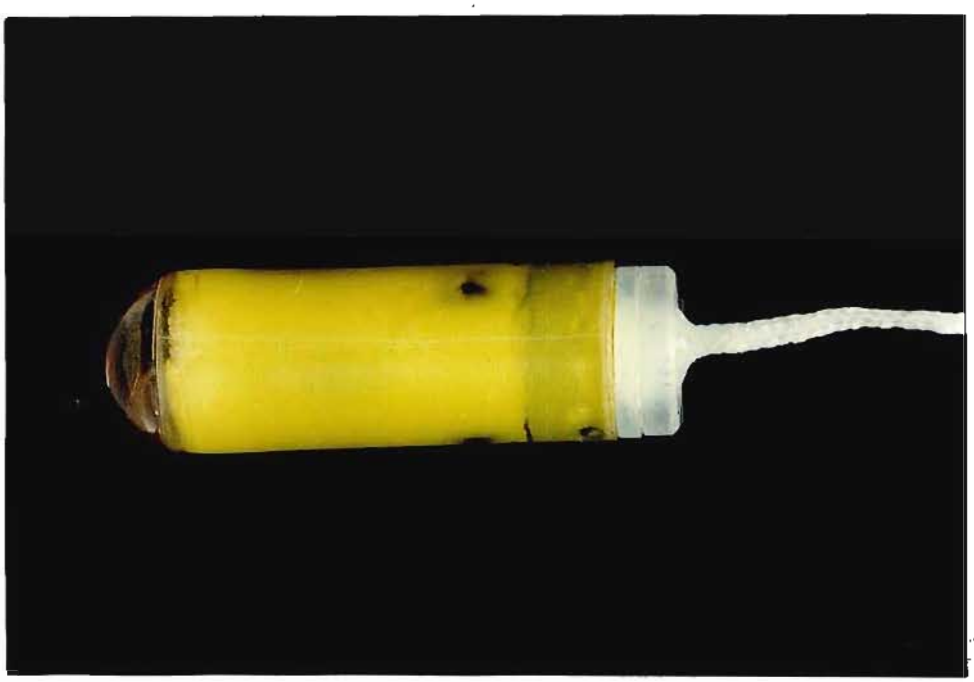


ILLUSTRATION 2.6 Oesophageal pH: Radiotelemetry Pill.

high pressure zone. The radiotelemetry pill has a self-contained sodium chloride reservoir as a reference electrode. Radiosignals from the pill are received by a ferric bar aerial worn around the chest of the patient (Illustration 2.7). The response time for the pill is one second. Changes in the pH were recorded by a microprocessor receiving unit worn on a wastebelt (Illustration 2.8). All patients underwent pH monitoring in their routine home or work environment for 18 to 24 hours (Illustration 2.9). The portable receiving unit contains an 8 bit Motorola microprocessor and a 32K random access memory for digital data storage. Oesophageal pH was recorded every 10 seconds and stored in the microprocessor receiving unit. At the conclusion of the ambulatory testing the data is transferred into an IBM computer for analysis and permanent disc storage. The microprocessor incorporates an event button coupled with a 16 character dot matric liquid crystal display which allows the patient to indicate specific activities or symptoms such as meals, position (erect or supine) or pain. The button enters an event specific code into the computer memory simultaneously with the oesophageal pH and time; thus precise correlation of pH and selected events is possible. A segment from a computer generated plot of pH data with events as indicated by the patient is shown in Figure 2.3. Patients were unrestricted as to the number of meals or supine episodes allowed during testing and were encouraged to follow their usual daily activity routine. Instructions were given to avoid food and beverages with high acid content and a diary was kept by each patient listing items consumed during testing.

Computer based analysis schemes were developed for interpretation of the oesophageal pH data. Two methods of evaluation were used. The first method was based on individual reflux events. The onset of a reflux event was defined as a drop in oesophageal pH to below four and its termination when the pH reverted to four or above. The frequency and average duration in minutes of these reflux events were reported along with the total time in minutes

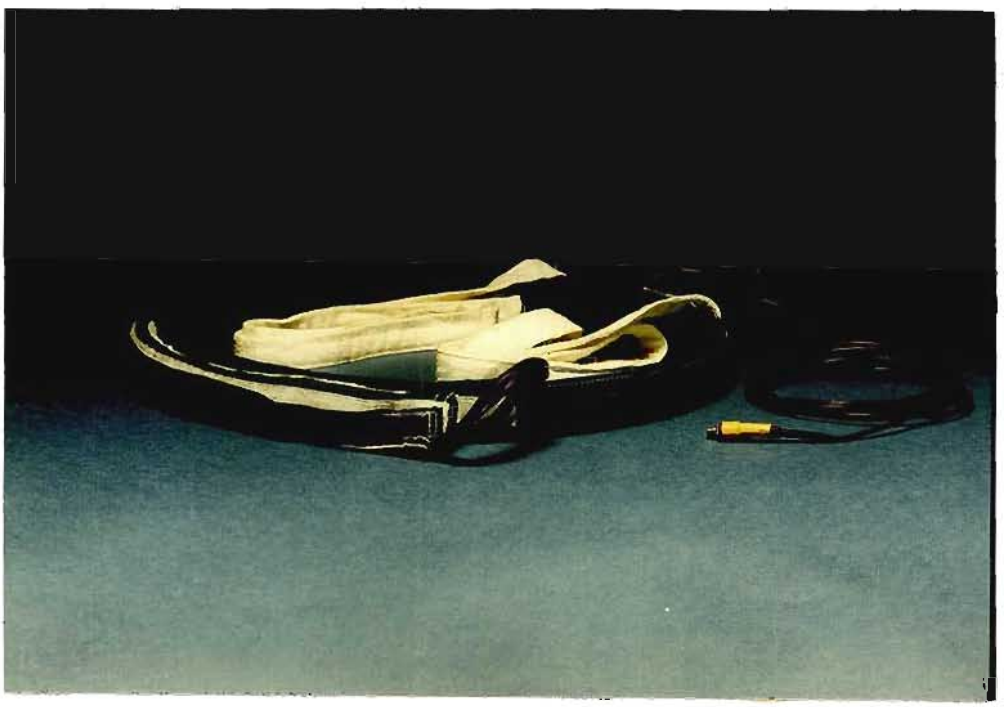


ILLUSTRATION 2.7 Oesophageal pH Ferric Bar Aerial.

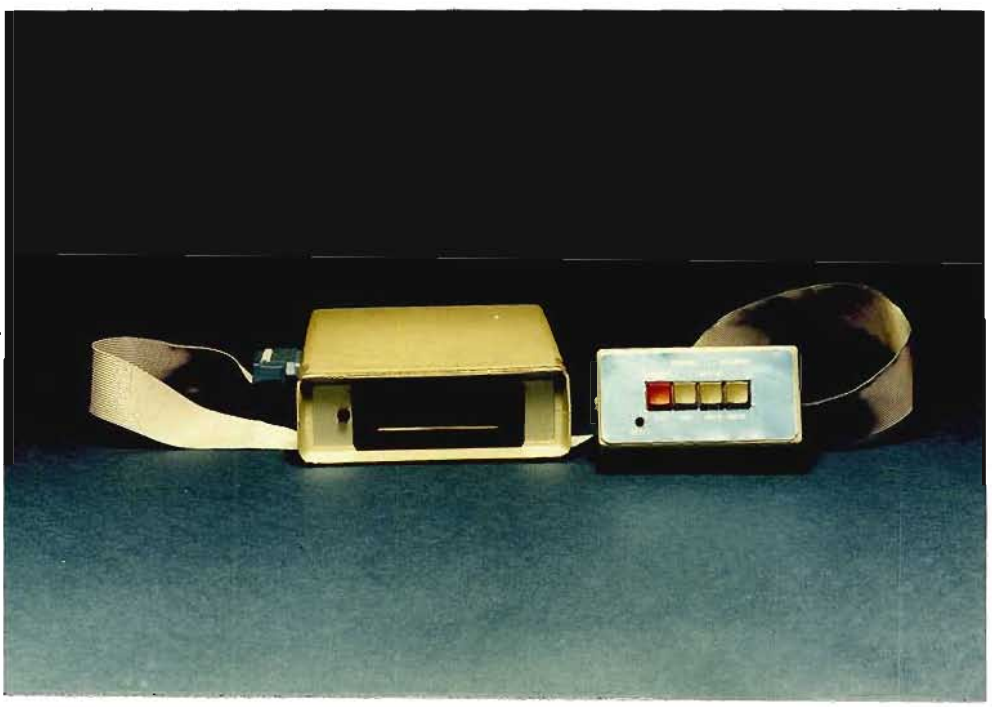


ILLUSTRATION 2.8 Oesophageal pH: Microprocessor receiving unit.

ILLUSTRATION 2.9 pH monitoring equipment *in situ*.

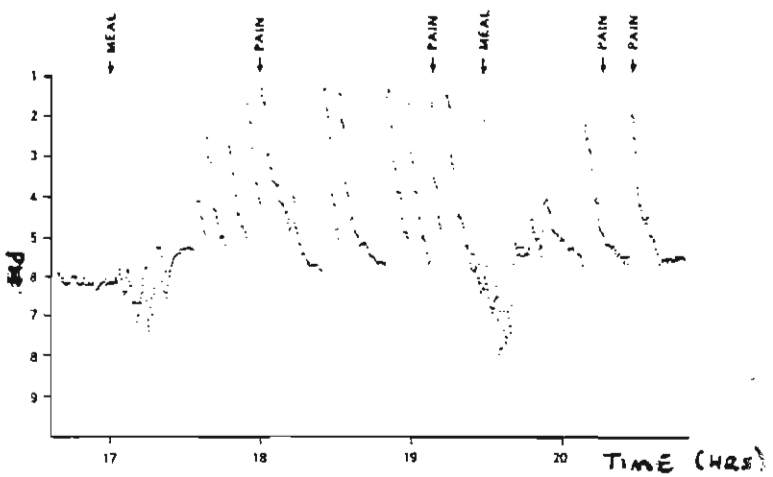


FIGURE 2.3 pH data with events.

per hour of oesophageal exposure to pH <4. A separate analysis was done for erect and supine periods (Table 2.1). The second method of analysis was based on total acid exposure (pH <4). This method is recommended by Schindlbeck *et al.* (1987) and by Johnsson *et al.* (1987) as it is accurate, simple to measure and understand and obviates the need to define or count reflux episodes. Separate determinations were carried out for supine and erect periods. A graphic representation of cummulative and exposure was obtained for each patient (Figure 2.4). An individual record was regarded as abnormal if the patient shaded area crossed the mean plus three standard deviations.

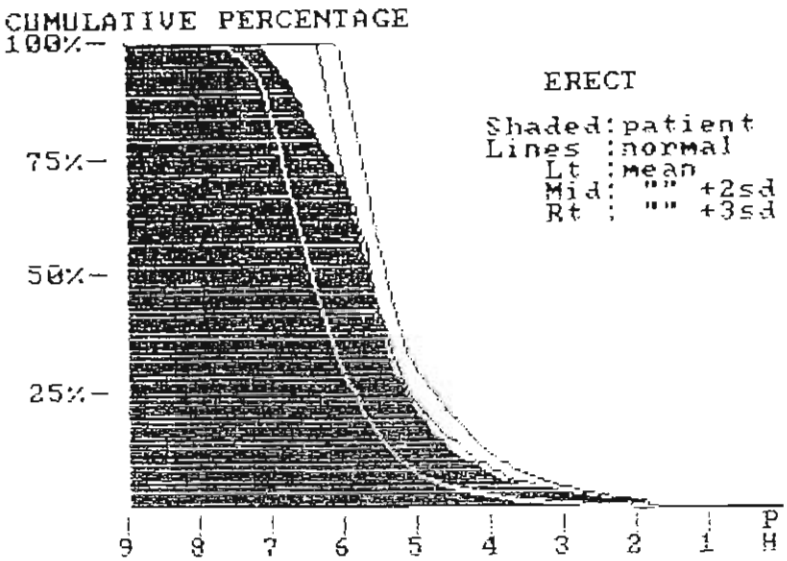
One hundred patients were recruited into this study, strictly according to the eligibility criteria outlined at the beginning of this chapter. As a control group fifty of these patients were treated with the present standard treatment of reflux oesophagitis, ie. Ranitidine 150 mg twice a day. The rest were treated with Rioprostil (E1 methyl prostaglandin analogue) 300 μg twice a day. This dose reduces the basal acid secretions by 54%, meal stimulated acid secretion by 70% and pentagastrin stimulated gastric acid secretion by 40% (Demol, 1985). The study was conducted in a double-blind fashion, patients being randomly assigned by a computer generated randomisation list.

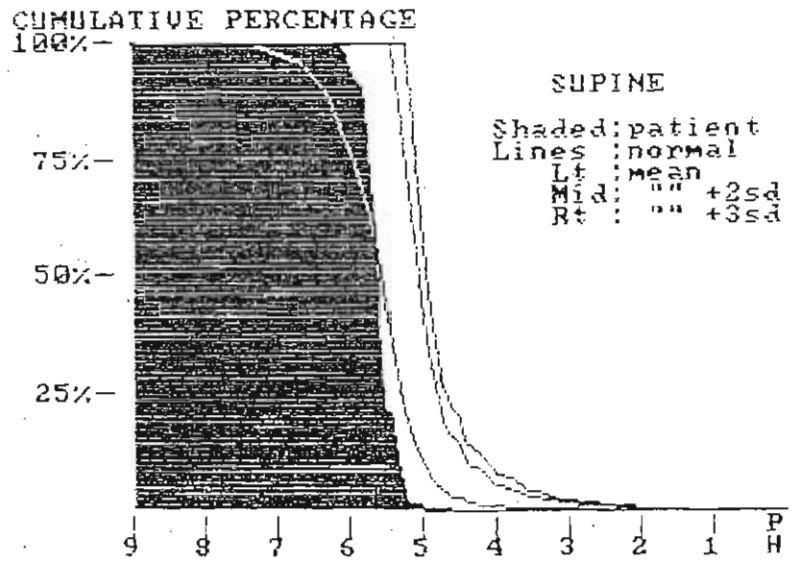
Patients were treated for twelve weeks and ethical approval for the study was granted by the Tayside Health Board Ethics Committee.

TABLE 2.1 Individual reflux events analysed.

	Erect	Supine	Total
Time pH <4 (min)	4.46	0.00	2.33
Number of events	1.97	0.00	1.03
Duration per event (min)	2.26	0.00	2.26
Reflux pattern (no of events)			
- <5 mins	1.88	0.00	0.98
- > 5 mins	0.09	0.00	0.05
Longest event (min)	8.00	0.00	8.00

- Acid reflux = pH <4
- All data standardised for one hour
- Score 16.91





PERCENTAGE OF DATA BELOW PH VALUE

› =2 SD above mean
›› =3 SD above mean

pH	9	8	7	6	5	4	3	2	1
RECORD:	0								
ERECT	100.0	100.0	96.7	70.4	20.1	7.5	3.1	0.2	0.0
SUPINE	100.0	100.0	100.0	94.7	0.8	0.0	0.0	0.0	0.0
TOTAL	100.0	100.0	98.3	82.1	10.9	3.9	1.6	0.1	0.0

FIGURE 2.4 Comulative acid exposure.

CHAPTER 3
RESULTS

One hundred patients were recruited into the study. Fifty patients were randomly allocated by computer to each treatment group, viz. H_2 antagonists (Ranitidine) or prostaglandins (Rioprostil). Eleven patients were excluded from the Rioprostil arm (Table 3.1). This was due to; development of adverse drug reactions (n=5) (diarrhoea 4, skin rash 1), protocol violation (n=1), discovery of significant cardiovascular disease (n=3) and loss to follow-up (n=2). Seven patients were excluded from the Ranitidine group due to; adverse drug reactions (n=1) (skin rash), haematemesis from an ulcerated oesophagus requiring additional therapy (n=1), intercurrent illness which required hospitalisation (n=1), subsequent diagnosis of a duodenal ulcer (n=1), and significant cardiovascular disease (n=4) (Table 3.1).

TABLE 3.1 Summary of patients excluded from analysis.

COMMENT	RIOPROSTIL	RANITIDINE	TOTAL
Patients admitted	50	50	100
Patients excluded			
Adverse drug reactions	5	1	6
Protocol violation	1	-	1
Loss to follow-up	2	-	2
Haematemesis	-	1	1
Duodenal ulceration	-	1	1
Significant cardio-vascular disease	3	4	7
Patients analysed	39	43	82

Thirty-nine patients in the Rioprostil group and 43 patients from the Ranitidine group were evaluable. The groups were well matched for the demographic data collected (Table 3.2). There was a preponderance of males in the Rioprostil group and a female preponderance in the

Ranitidine group but the distribution of the sexes did not reach significance (P=0.230, Yates corrected Chi-squared test).

TABLE 3.2 Demographic data.

	RIOPROSTIL	RANITIDINE
Mean age years (range)	42.4 (18-78)	48.2 (19-76)
Sex ratio (M:F)	23:16	18:25
Height in metres (range)	1.69 (1.55-1.85)	1.65 (1.46-1.91)
Weight in kg (range)	68.76 (45-104)	65.15 (45-98.4)
Duration of symptoms in years (range)	2.5 (0.25-34)	2 (0.25-20)
Number of smokers	17	14
Number of alcohol consumers	14	12
Number of hiatal hernia	19	17
	9 (5M:4F)	11 (5M:6F)

The results of the symptom assessment of heartburn, regurgitation and dysphagia are demonstrated in Tables 3.3 to 3.8. The total De Meester symptom score results are demonstrated in Tables 3.9, 3.10 and Figure 3.1.

TABLE 3.3 Patients with heartburn.

	RIOPROSTIL	RANITIDINE	TOTAL
On admission			
None	03 (06.0%)	02 (04.0%)	05 (05.0%)
Minimal	34 (68.0%)	38 (76.0%)	72 (72.0%)
Moderate	13 (26.0%)	10 (20.0%)	21 (23.0%)
Total	50 (100%)	50 (100%)	100 (100%)
After 4 weeks			
None	02 (04.4%)	06 (12.5%)	08 (08.6%)
Minimal	25 (55.6%)	35 (72.9%)	60 (64.5%)
Moderate	14 (08.9%)	07 (14.6%)	21 (22.6%)
Severe	04 (08.9%)	0	04 (04.3%)
Total	44 (100%)	48 (100%)	93 (100%)
After 8 weeks			
None	06 (14.0%)	10 (21.7%)	16 (18.0%)
Minimal	28 (65.1%)	29 (63.0%)	57 (64.0%)
Moderate	07 (16.3%)	07 (15.2%)	14 (15.7%)
Severe	02 (04.7%)	0	02 (02.2%)
Total	43 (100%)	48 (100%)	89 (100%)
After 12 weeks			
None	05 (12.8%)	16 (37.2%)	21 (25.6%)
Minimal	28 (71.7%)	25 (58.1%)	53 (64.6%)
Moderate	05 (12.8%)	02 (04.7%)	07 (08.5%)
Severe	01 (02.5%)	0	01 (01.2%)
Total	39 (100%)	43 (100%)	82 (100%)

TABLE 3.4 Change of heartburn during treatment.

	RIOPROSTIL	RANITIDINE	TOTAL
Severity after Week 4			
Decreased	28 (62.2%)	44 (91.7%)	72 (77.4%)
Unchanged	16 (35.6%)	04 (08.3%)	20 (21.5%)
Increased	01 (02.2%)	0 (0%)	01 (01.1%)
Total	45 (100%)	48 (100%)	93 (100%)
Severity after Week 8			
Decreased	34 (79.1%)	40 (87.0%)	74 (83.1%)
Unchanged	09 (20.9%)	06 (13.0%)	15 (16.0%)
Total	43 (100%)	46 (100%)	89 (100%)
Severity after Week 12			
Decreased	33 (84.6%)	42 (97.7%)	75 (91.5%)
Unchanged	06 (15.4%)	01 (02.3%)	07 (08.5%)
Total	39 (100%)	43 (100%)	82 (100%)

* Severity of heartburn was improved by both Rioprostil and Ranitidine; Ranitidine being more effective.

TABLE 3.5 Patients with regurgitation.

	RIOPROSTIL	RANITIDINE	TOTAL
On admission			
None	08 (16.0%)	15 (30.0%)	23 (23.0%)
Minimal	29 (58.0%)	27 (54.0%)	56 (56.0%)
Moderate	13 (26.0%)	08 (16.0%)	21 (21.0%)
Total	50 (100%)	50 (100%)	100 (100%)
After 4 weeks			
None	19 (42.2%)	22 (44.9%)	41 (43.6%)
Minimal	27 (48.9%)	27 (55.1%)	49 (52.1%)
Moderate	04 (08.9%)	0	04 (04.3%)
Total	50 (100%)	49 (100%)	94 (100%)
After 8 weeks			
None	19 (44.2%)	32 (69.6%)	51 (57.3%)
Minimal	22 (51.2%)	14 (30.4%)	36 (40.4%)
Moderate	02 (04.7%)	0	02 (02.2%)
Total	43 (100%)	46 (100%)	89 (100%)
After 12 weeks			
None	20 (51.2%)	29 (67.4%)	49 (59.7%)
Minimal	17 (43.5%)	14 (32.5%)	31 (37.8%)
Moderate	02 (05.1%)	0	02 (02.4%)
Total	49 (100%)	43 (100%)	82 (100%)

TABLE 3.6 Change of regurgitation during treatment.

	RIOPROSTIL	RANITIDINE	TOTAL
Severity after Week 4			
Decreased	21 (46.7%)	16 (32.7%)	37 (39.4%)
Unchanged	21 (46.7%)	30 (61.2%)	51 (54.3%)
Increased	03 (06.7%)	3 (06.1%)	06 (06.4%)
Total	45 (100%)	49 (100%)	94 (100%)
Severity after Week 8			
Decreased	22 (51.2%)	21 (45.7%)	43 (48.3%)
Unchanged	17 (39.5%)	24 (52.2%)	41 (46.1%)
Increased	04 (09.3%)	01 (02.2%)	05 (05.6%)
Total	43 (100%)	46 (100%)	89 (100%)
Severity after Week 12			
Decreased	21 (54.0%)	20 (46.5%)	41 (50.0%)
Unchanged	16 (41.0%)	22 (51.0%)	38 (46.3%)
Increased	02 (05.0%)	01 (02.5%)	03 (03.7%)
Total	39 (100%)	43 (100%)	82 (100%)

* Both Rioprostil and Ranitidine improved regurgitation, Rioprostil being more effective.

TABLE 3.7 Patients with dysphagia.

	RIOPROSTIL	RANITIDINE	TOTAL
On admission			
None	33 (66.0%)	35 (70.0%)	68 (68.0%)
Minimal	15 (30.0%)	11 (22.0%)	26 (26.0%)
Moderate	02 (04.0%)	04 (08.0%)	06 (06.0%)
Total	50 (100%)	50 (100%)	100 (100%)
After 4 weeks			
None	35 (77.8%)	42 (85.7%)	77 (81.9%)
Minimal	10 (22.2%)	06 (12.2%)	16 (17.0%)
Moderate	0	01 (02.0%)	01 (01.0%)
Total	45 (100%)	49 (100%)	94 (100%)
After 8 weeks			
None	36 (83.7%)	40 (87.0%)	76 (85.4%)
Minimal	05 (11.6%)	06 (13.0%)	11 (12.4%)
Moderate	02 (04.7%)	0	04 (02.2%)
Total	24 (100%)	46 (100%)	89 (100%)
After 12 weeks			
None	31 (79.4%)	38 (88.3%)	69 (84.1%)
Minimal	08 (20.5%)	05 (11.6%)	13 (15.8%)
Total	39 (100%)	43 (100%)	82 (100%)

TABLE 3.8 Change of dysphagia during treatment.

	RIOPROSTIL	RANITIDINE	TOTAL
Severity after Week 4			
Decreased	11 (24.4%)	08 (16.3%)	19 (20.2%)
Unchanged	31 (68.9%)	41 (83.7%)	72 (76.6%)
Increased	03 (06.7%)	0 (0%)	03 (03.2%)
Total	45 (100%)	49 (100%)	94 (100%)
Severity after Week 8			
Decreased	13 (30.2%)	09 (19.6%)	22 (24.7%)
Unchanged	27 (62.8%)	37 (80.4%)	64 (71.9%)
Increased	03 (07.0%)	0 (0%)	03 (03.4%)
Total	43 (100%)	46 (100%)	89 (100%)
Severity after Week 12			
Decreased	11 (28.0%)	09 (21.0%)	20 (24.3%)
Unchanged	26 (66.5%)	33 (76.7%)	59 (72.1%)
Increased	02 (0%)	01 (02.3%)	03 (03.6%)
Total	43 (100%)	43 (100%)	82 (100%)

* Both Rioprostil and Ranitidine improved dysphagia, Rioprostil being more effective.

TABLE 3.9 Median and range (in brackets) of total symptom score (heartburn, regurgitation and dysphagia).

	RIOPROSTIL	RANITIDINE	p
On admission	3 (2-6)	3 (1-6)	NS
After 4 weeks	2 (0-6)	2 (0-5)	NS
After 8 weeks	2 (0-5)	1 (0-3)	NS
After 12 weeks	1 (0-5)	1 (0-4)	$p < 0.05$

* Both drugs improved the total symptom score, Ranitidine being the superior

TABLE 3.10 Change of total symptomatic score during treatment.

	RIOPROSTIL	RANITIDINE	TOTAL
Severity after Week 4			
Decreased	34 (75.6%)	43 (89.6%)	77 (82.8%)
Unchanged	10 (22.2%)	05 (10.4%)	15 (16.1%)
Increased	01 (02.2%)	0 (0%)	01 (01.1%)
Total	45 (100%)	48 (100%)	93 (100%)
Severity after Week 8			
Decreased	36 (83.7%)	43 (93.5%)	79 (88.8%)
Unchanged	06 (14.0%)	03 (06.5%)	09 (10.1%)
Increased	01 (02.3%)	0 (0%)	01 (01.1%)
Total	43 (100%)	46 (100%)	89 (100%)
Severity after Week 12			
Decreased	39 (90.0%)	43 (100%)	78 (95.1%)
Unchanged	03 (07.5%)	0 (0%)	03 (03.6%)
Increased	01 (02.5%)	0 (0%)	01 (01.3%)
Total	43 (100%)	43 (100%)	82 (100%)

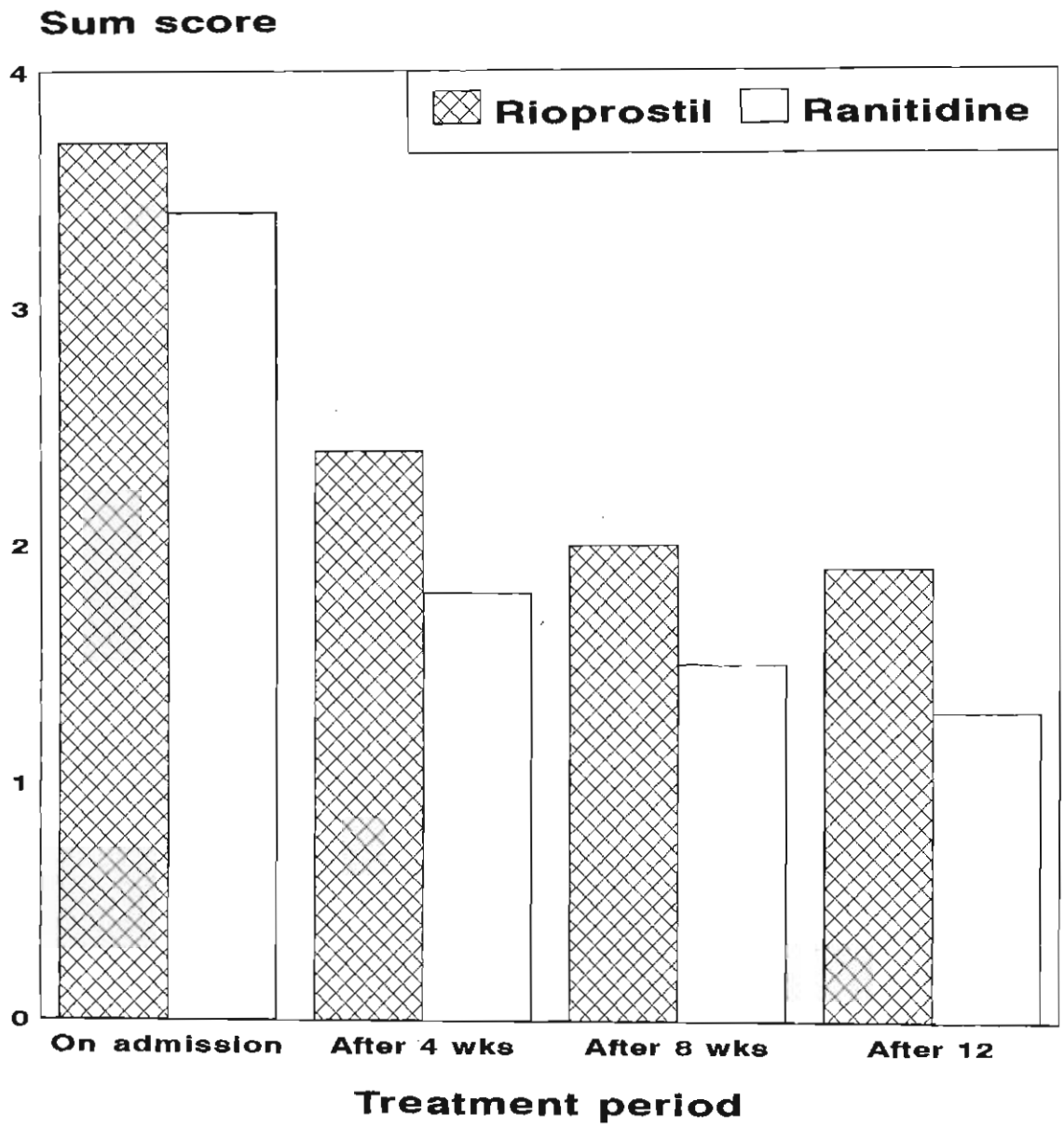


FIGURE 3.1 Total symptomatic scores (heartburn, regurgitation and dysphagia).

The results of the endoscopic evaluation of the severity of the oesophagitis performed on admission and on week 12 of treatment are shown in Table 3.11.

TABLE 3.11 Endoscopic appearances on admission and after treatment.

	RIOPROSTIL	RANITIDINE	TOTAL
On admission			
Normal mucosa	06 (15%)	05 (12%)	11 (13.4%)
Minimal oesophagitis	21 (54%)	22 (51%)	43 (52.4%)
Moderate oesophagitis	09 (23%)	09 (21%)	18 (21.9%)
Severe oesophagitis	03 (08%)	07 (16%)	10 (12.2%)
Total	39 (100%)	43 (100%)	82 (100%)
After 12 weeks			
Normal mucosa	20 (51%)	29 (67%)	49 (59.7%)
Minimal oesophagitis	13 (33%)	10 (23%)	23 (28.0%)
Moderate oesophagitis	05 (13%)	02 (05%)	07 (08.5%)
Severe oesophagitis	01 (03%)	02 (05%)	03 (03.6%)
Total	39 (100%)	43 (100%)	82 (100%)

There was significant endoscopic improvement in both groups between admission and after 12 weeks of therapy ($p < 0.01$ for Rioprostil and $p < 0.0001$ for Ranitidine, Chi-squared test). However, significantly more of the patients treated with Ranitidine responded to the treatment

with endoscopic improvement than did patients treated by Rioprostil ($p < 0.01$ Chi-squared test).

In the Rioprostil group 17 patients were endoscopically improved, 22 patients were unchanged (6 patients had normal mucosa on admission and remained so at the end of therapy). By contrast in the Ranitidine group 29 patients improved endoscopically; 13 patients were unchanged (4 patients had normal mucosa on admission, this remained unchanged at the end of therapy); 1 patient had more severe oesophagitis at the end of 12 weeks therapy. The endoscopic healing rates were 12/33 (36.4%) and 23/36 (63.9%) in the Rioprostil and Ranitidine arms respectively. These results are shown in tabloid form (Table 3.12).

TABLE 3.12 Endoscopic changes during treatment (admission to week 12).

	RIOPROSTIL	RANITIDINE	TOTAL
Severity of oesophagitis			
Decreased	17 (43.5%)	29 (67.4%)	46 (56.0%)
Unchanged	22 (56.4%)	13 (30.2%)	35 (42.6%)
Increased	0	01 (02.3%)	01 (01.2%)
Total	39 (100%)	43 (100%)	82 (100%)

Histological results are illustrated in Table 3.13. Overall, in the Rioprostil group, 21 patients were improved histologically, 15 patients showed no change (1 patient's biopsy showed no inflammation on admission and at the end of therapy) and 3 patient's biopsies showed more inflammation at the end of therapy than on admission (Table 3.14). In the Ranitidine arm, 23 patients were histologically improved, 16 patients were unchanged (1 patient's biopsy showed no inflammation on admission and at the end of therapy) and in 2 patients the inflammation was more severe at the end of therapy than on admission (Table 3.14).

TABLE 3.13 Histological evaluation of the oesophageal mucosal inflammation.

	RIOPROSTIL	RANITIDINE	TOTAL
On admission			
Normal mucosa	03 (07.0%)	01 (02.0%)	04 (04.8%)
Minimal inflammation	25 (64.0%)	27 (63.0%)	52 (63.4%)
Moderate inflammation	08 (21.0%)	09 (21.0%)	17 (20.7%)
Severe inflammation	03 (08.0%)	06 (14.0%)	09 (10.9%)
Total	39 (100%)	43 (100%)	82 (100%)
After 12 weeks			
Normal mucosa	15 (39.0%)	16 (39.0%)	31 (38.7%)
Minimal inflammation	13 (33.0%)	10 (23.0%)	23 (50.0%)
Moderate inflammation	03 (08.0%)	04 (10.0%)	07 (08.7%)
Severe inflammation	01 (02.0%)	01 (02.0%)	02 (02.5%)
Total	32 (100%)	31 (100%)	63 (100%)

TABLE 3.14 Histological changes between admission and week 12.

	RIOPROSTIL	RANITIDINE	TOTAL
Severity of inflammation			
Decreased	21	23	44
Unchanged	15	16	31
Increased	03	02	05
Total	39	41	80

A significant histological improvement was observed in both groups between admission and end of therapy ($p < 0.05$ for the Ranitidine and Rioprostil arms, Chi-squared test).

Oesophageal function was assessed by radionucleide egg transit, 24-hour pH studies and oesophageal manometry. The results of the egg transit in the proximal, middle and distal oesophagus together with total egg transit times are demonstrated in Tables 3.15-3.18.

TABLE 3.15 Oesophageal transit time: upper third (sec).

	RIOPROSTIL	RANITIDINE
Initial (Week 0)		
Number of patients	39	41
Mean	19.1	26.4
Median	7	7
Standard deviation	32.5	53.2
Minimum	4	5
Maximum	170	240
Week 12		
Number of patients	39	41
Mean	30.9	19.4
Median	7	7
Standard deviation	47.4	39.7
Minimum	4	4
Maximum	240	212

No significant change in transit times in proximal third pre- and post-treatment with both Rioprostil and Ranitidine ($p > 0.05$ Chi-square).

TABLE 3.16 Oesophageal transit time: mid third (sec).

	RIOPROSTIL	RANITIDINE
Initial (Week 0)		
Number of patients	39	41
Mean	66.2	67.1
Median	25	10
Standard deviation	78.6	88.2
Minimum	5	6
Maximum	240	240
Week 12		
Number of patients	39	41
Mean	48.8	48.4
Median	8	10
Standard deviation	77.9	73.1
Minimum	4	6
Maximum	240	240

No significant change in transit times between week 0 and week 12 in both Rioprostil and Ranitidine groups ($p > 0.05$ Chi-square).

TABLE 3.17 Oesophageal transit time: lower third (sec).

	RIOPROSTIL	RANITIDINE
Initial (Week 0)		
Number of patients	39	41
Mean	50.8	63.95
Median	10	11
Standard deviation	85.2	93.9
Minimum	6	6
Maximum	240	240
Week 12		
Number of patients	41	41
Mean	31.8	44.1
Median	9	11
Standard deviation	69.3	76.2
Minimum	7	6
Maximum	240	240

No significant change in transit times between pre- and post-treatment with Rioprostil and Ranitidine ($p > 0.05$ Chi-square).

TABLE 3.18 Oesophageal transit time: Total in sec.

	RIOPROSTIL	RANITIDINE
Initial (Week 0)		
Number of patients	39	41
Mean	76.5	84.8
Median	35	30
Standard deviation	85.3	92.9
Minimum	6	7
Maximum	240	240
Week 12		
Number of patients	39	41
Mean	55.0	61.1
Median	13	15
Standard deviation	76.6	80.4
Minimum	8	5
Maximum	240	240

No significant change in transit times between week 0 and week 12 in both Rioprostil and Ranitidine groups ($p > 0.05$ Chi-square).

* Rioprostil was not found to be superior to Ranitidine in improving transit times between Week 0 and Week 12.

Tables 3.19 and 3.20 show the 24-hour ambulatory pH monitoring with Rioprostil and Ranitidine respectively. The figures included represent the median value of the variable.

TABLE 3.19 24-hour pH monitoring (Rioprostil).

		ADMISSION	WEEK 12	p
Oesophageal exposure to pH <4 (minutes)	Erect	2.76	4.46	NS
	Supine	0.51	0.4	NS
	Total	2.33	3.75	NS
Number of reflux episodes	Erect	2.0	2.75	NS
	Supine	0.22	0.27	NS
	Total	1.14	1.53	NS
Average duration of reflux episodes (minutes)	Erect	1.23	1.52	NS
	Supine	2.15	1.58	NS
	Total	1.62	2.01	NS
Number of reflux episodes >5 minutes	Erect	0.08	0.09	NS
	Supine	0	0	NS
	Total	0.05	0.1	NS
Duration of longest event	Erect	5.0	5.83	NS
	Supine	3.5	2.33	NS
	Total	9.33	8.0	NS

NS = no significant difference.

No significant difference was found on any of the pH parameters after 12 weeks of Rioprostil therapy.

TABLE 3.20 24-hour pH monitoring (Ranitidine).

		ADMISSION	WEEK 12	p
Oesophageal exposure to pH <4 (minutes)	Erect	4.24	2.84	NS
	Supine	1.53	0	S
	Total	4.08	2.4	NS
Number of reflux episodes	Erect	2.39	1.81	NS
	Supine	0.43	0	S
	Total	1.6	1.08	NS
Average duration of reflux episodes (minutes)	Erect	1.53	1.88	NS
	Supine	2.77	0	S
	Total	2.14	1.56	NS
Number of reflux episodes >5 minutes	Erect	0.1	0.09	NS
	Supine	0.1	0	S
	Total	0.14	0.05	NS
Duration of longest event	Erect	6.75	5.75	NS
	Supine	5.59	0	S
	Total	11.5	7.5	NS

NS = no significant difference.

S = significant difference.

Ranitidine therapy resulted in a significant reduction in the time that the lower oesophagus was exposed to pH <4 and in the number of reflux events in the supine position ($p < 0.05$). In addition, after 12 weeks of therapy, Ranitidine resulted in a significant ($p < 0.05$) reduction in the occurrence and duration of reflux events in the supine posture.

TABLE 3.21 24 hour pH reflux test* using De Meesters scores (admission - Week 12).

	RIOPROSTIL	RANITIDINE	TOTAL
Test on admission			
Negative	23 (47.9%)	22 (44.9%)	45 (46.4%)
Positive	25 (52.1%)	27 (55.1%)	52 (53.6%)
Total	48 (100%)	49 (100%)	97 (100%)
Test after 12 weeks			
Negative	11 (29.7%)	22 (53.7%)	33 (42.3%)
Positive	26 (70.3%)	19 (46.3%)	45 (57.7%)
Total	37 (100%)	41 (100%)	78 (100%)

* test = negative, if sum of scores <=17.92
test = positive, if sum of score >17.92

A large percentage of patients, 46.4%, had negative pH test scores on admission.

TABLE 3.22 Change of 24 hour pH reflux test (admission - Week 12).

	24 hour pH reflux test*			
	Pos → Neg	Pos → Pos Neg → Neg	Neg → Pos	Total
Rioprostil	01 (02.7%)	29 (78.4%)	07 (18.9%)	37 (100%)
Ranitidine	06 (14.6%)	32 (78.0%)	03 (07.3%)	41 (100%)

* test = negative, if sum of scores <=17.92
test = positive, if sum of score >17.92

Exact permutation test for ordered categories: p = 0.0451

Ranitidine therapy resulted in test scores changing from positive to negative in 6 patients (14.6%). In 7 patients (18.9%) on Rioprostil therapy test scores changed from negative to positive.

TABLE 3.23 Change of sum of scores (admission - Week 12)

	RIOPROSTIL	RANITIDINE	TOTAL
Sum of scores			
Decreased	14 (37.8%)	20 (48.8%)	34 (43.6%)
Increased	23 (62.2%)	21 (51.2%)	44 (56.4%)
Total	37 (100%)	41 (100%)	78 (100%)

Lower oesophageal sphincter pressure and oesophageal contractility was determined using oesophageal manometry.

TABLE 3.24 Oesophageal manometry: Lower oesophageal sphincter pressure (mmHg).

	RIOPROSTIL	RANITIDINE
Initial (Week 0)		
Number of patients	41	40
Mean	12.4	12.7
Median	12	11
Standard deviation	5.3	6.7
Minimum	4	5
Maximum	30	40
Week 12		
Number of patients	34	33
Mean	12.4	12.7
Median	11	11
Standard deviation	5.7	7.8
Minimum	5	5
Maximum	29	40

No significant difference was found in the lower oesophageal sphincter pressure before and after treatment with both Rioprostil and Ranitidine ($p > 0.05$ Chi-square test).

Contractions of the oesophagus was graded according to criteria by Benjamin *et al.* (1983). These criteria (Table 3.25) divide patients into those having a normal manometry, a primary motility disorder, or a nonspecific motor disorder.

One patient referred to the study with symptoms of heartburn and dysphagia was found to have achalasia. This patient was referred for appropriate treatment and excluded from the study.

The majority of patients had normal manometry tracings (Tables 3.26-27). No change was noted in those patients with spontaneous contractions despite treatment. In 4 patients some improvement in manometric tracings was found after treatment (Table 3.28).

The total amplitude and duration of contractions was also measured manometrically (Table 3.29).

There was no statistical difference in the total amplitude and duration of the contractions before and after treatment with Ranitidine and Rioprostil.

TABLE 3.25 Criteria for manometric diagnosis (from Benjamin *et al.*, 1983).

I. ***Normal***

1. LES pressure 10-26 mmHg (x ±2 SD) with normal relaxation
2. Mean peristaltic amplitude in the distal esophagus 50-110 mmHg (x ±2 SD)
3. Absence of spontaneous, repetitive, or simultaneous contractions
4. Single wave forms (with not more than 2 peaks)
5. Mean duration of peristaltic waves in the distal esophagus 1.9 ± 5.5 s (x ±2 SD)

II. ***Primary motility disorders***

1. *Achalasia*
   a. Aperistalsis in esophageal body
   b. Incomplete LES relaxation
   c. Elevated LES pressure (>26 mmHg)
   d. Increased intraesophageal baseline pressures relative to gastric baseline

2. *Diffuse esophageal spasm (DES)*
   a. Simultaneous (nonperistaltic) contractions
      i. repetitive (at least 3 peaks) contractions
      ii. increased duration (>5.5 s)

   Spontaneous contractions

   Periods of normal peristalsis

   Contractions may be of increased amplitude

3. *"Nutcracker esophagus"*
   a. Mean peristaltic amplitude (10 "wet" swallows) in the distal esophagus >120 mmHg
   b. Increased mean duration of contractions (>5.5 s) often found
   c. Normal peristaltic sequence

III. ***Nonspecific esophageal motility disorders (NEMD)***

Abnormal manometry representing primary esophageal motor disorders other than achalasia, DES, or "nutcracker esophagus"

1. *Hypertensive LES*
   a. LES pressure >26 mmHg with normal relaxation
   b. Normal esophageal peristalsis

2. *Decreased or absent amplitude of esophageal peristalsis*
   a. Normal LESP
   b. Normal LES relaxation

3. *Other abnormalities of peristaltic sequence (including any combination of the following)*
   a. Abnormal wave forms
   b. Isolated simultaneous contractions
   c. Isolated spontaneous contractions
   d. Normal peristaltic sequence maintained
   e. LES normal

LES = lower oesophageal sphincter.

TABLE 3.26 Oesophageal manometry (Week 0): abnormal wave forms and contractions.

	RIOPROSTIL		RANITIDINE	
TOTAL		50		50
Abnormal				
- spontaneous contractions	01)		02)	
- abnormal wave forms	08)	09	11)	13
Failed/refused manometry		09		10

TABLE 3.27 Oesophageal manometry (Week 12): abnormal wave forms and contractions.

	RIOPROSTIL		RANITIDINE	
TOTAL		50		50
Abnormal				
- spontaneous contractions	01)		02)	
- abnormal wave forms	04)	05	08)	10
Failed/refused manometry		16		18

TABLE 3.28 Oesophageal manometry: abnormal wave forms and spontaneous contractions.

	RIOPROSTIL	RANITIDINE	TOTAL
No change	3	8	11
Improvement	3	1	4
Deterioration	2	2	4

TABLE 3.29 Total amplitude and duration of contractions for all patients

	MEAN	(SD)*	NUMBER	p VALUE
Amplitude (mmHg)				
Pre-	44.97	(8.99)	82	)
Post-	44.01	(8.41)	67	) ns
Diff	0.97	(6.63)		
Duration (Sec)				
Pre-	3.84	(1.61)	82	
Post-	3.65	(1.22)	67	
Diff	0.11	(0.92)		ns

* SD - Standard Deviation

Differences between pre- and post- within each group were not statistically significant.

Paired T-test was used to compare pre- and post- values within the groups.

TABLE 3.30 Association between hiatal hernia and reflux oesophagitis

	ABSENT	PRESENT	TOTAL
Rioprostil	38 (76.0%)	12 (24.0%)	50
Ranitidine	37 (75.5%)	12 (24.5%)	49
Total	75 (75.8%)	24 (24.2%)	99

Only 24.2% of our patients with reflux oesophagitis had associated hiatal hernia.

No significant difference was found between the laboratory values (full blood count, liver function tests, urea and electrolytes) of either treatment group when the pre-treatment levels were compared to those after 12 weeks of therapy.

CHAPTER 4
DISCUSSION

The purpose of this study was to examine the role of prostaglandins in patients with reflux disease. With its acid reducing, motility enhancing and cytoprotective qualities it should certainly be beneficial in patients with reflux oesophagitis. In this study the effect of prostaglandins on oesophageal reflux symptoms, macroscopic and microscopic healing, motility and pH studies was carefully monitored. The efficacy of the prostaglandin Rioprostil, was compared to a control group receiving the H_2 antagonist Ranitidine.

Heartburn, dysphagia and regurgitation individually and taken together using De Meesters symptom score showed improvement using both Rioprostil and Ranitidine. Symptoms were most improved in the first four weeks following commencement of treatment. Ranitidine and its effects on symptoms in patients with reflux oesophagitis has been studied previously (Table 4.1).

TABLE 4.1 Ranitidine and its effect on symptoms in patients with reflux oesophagitis.

	WEEKS	NUMBER	DOSE (mg/day)	SYMPTOM IMPROVEMENT
Goy *et al.* (1983)	6	37	300	nil
Wesdorp *et al.* (1983)	6	36	300	+
Lehtola *et al.* (1986)	12	41	450	+
Johansson *et al.* (1986)	8	38	300	+
Sontag *et al.* (1987)	6	284	300	+

All these studies have compared Ranitidine to placebo. Only Goy *et al*'s study failed to show any symptomatic improvement. The short duration of Goy *et al*'s study together with only one follow-up study and small number of patients (n=37) account for this difference. Unfortunately, direct comparison between the remaining studies and this study is difficult. This is due to failure of the different authors to give clear definitions to symptoms. Johannson *et al.* (1986) combines the symptoms of heartburn and regurgitation and lists pain separately. Lehtola *et al.* (1986) separates pain as to whether it is epigastric or retrosternal. In his study pain was considered equivalent to heartburn; regurgitation and dysphagia were investigated separately. Sontag *et al:* (1987) investigated heartburn frequency and severity only and Wesdorp *et al.* (1983) confusingly separated heartburn and pain as two separate symptoms. In this study, retrosternal discomfort, pain or burning is considered to be heartburn. Regurgitation and dysphagia are considered separately and the De Meester symptom score was used to grade symptoms. Wider use of this score would allow comparisons to be made between studies.

To further complicate matters different criteria are used by different authors to indicate success with treatment. Goy *et al.* (1983), Wesdorp *et al.* (1983) and Lehtola *et al.* (1986) use the grading of mild/moderate/severe and any improvement in the grade of symptoms is regarded as a success. Sontag *et al.* (1987) and Johansson *et al.* (1986) are more demanding in their criteria. Johansson *et al.* (1986) regards treatment as a failure even if their patients are improved but not satisfied. Sontag *et al.* (1987) regards treatment as a failure if there is less than 80% symptomatic improvement. It is thus not surprising that the efficacy rates for Ranitidine in the treatment of reflux oesophagitis vary widely:

Sontag *et al.* (1987)	34 %
Wesdorp *et al.* (1983)	42%
Johansson *et al.* (1986)	50%
Goy *et al.* (1983)	82%

The grading into mild/moderate/severe according to definite symptoms as used by Goy *et al.* (1983), Westdorp *et al.* (1983) and Lehtola *et al.* (1986) was used in this study.

There was a 97% improvement in heartburn, 46% improvement in regurgitation, and a 21% improvement in dysphagia using Ranitidine over a 12 week period. The symptoms of heartburn (retrosternal pain) correlated closely with Goy *et al*'s (1983) results. Westdorp *et al.* (1983) obtained a 63% improvement in regurgitation which also correlates with our results. Lehtola *et al.* (1986), Goy *et al.* (1983), Sontag *et al.* (1987) and Johansson *et al.* (1986) failed to investigate regurgitation and dysphagia as separate symptoms of reflux disease.

As prostaglandins have never previously been used to treat reflux oesophagitis, no comparisons can be made with the results of this study; further their efficacy in relieving the symptoms of reflux oesophagitis is unknown. This study interestingly showed prostaglandins to relieve reflux symptoms as shown in the Table 4.2 below, but not as effectively as Ranitidine.

TABLE 4.2 Improvement of symptoms.

SYMPTOM	RANITIDINE		RIOPROSTIL		P VALUE
Heartburn	42	97%	34	85%	P<0.05
Regurgitation	20	46%	22	55%	ns
Dysphagia	9	21%	11	27.5%	ns
TOTAL	43		40		

The percentage improvement in regurgitation and dysphagia was greater with Rioprostil. This is probably due to the motility enhancing effect of prostaglandins.

Both Rioprostil and Ranitidine showed a significant improvement in the total De Meester symptom score between the start and the end of 12 week therapy. Ranitidine was superior to Rioprostil in improving the total symptom score. Effective acid suppression appears to be an important factor in reducing the symptoms of reflux. The acid suppression capacity of Ranitidine has been shown to be superior to Rioprostil (Penston *et al.*, 1986).

Endoscopic improvement was similar to symptom improvement. Direct comparisons between available studies and this study again was difficult to make as different endoscopic criteria was used by different authors. Wesdorp *et al.* (1983) excluded patients with mild oesophagitis from his study; Johansson *et al.* (1986) and Meuwissen (1987) used the Savary-Millar classification and Sontag *et al.* (1987) and Goy *et al.* (1983) described their own grades of oesophagitis. Sontag *et al.* (1987) excluded patients with erythema of the distal oesophagus and Goy *et al.* (1983) based his classification on "streaks" in the mucosa. The classification used in this study is dependant on the Frierson (1990) classification. Six patients on Rioprostil and five patients on Ranitidine had normal endoscopy but were included in the study. All these patients had abnormal histology and symptoms of reflux disease. Reflux disease may well present with normal endoscopy appearance. Bytzer *et al.* (1993) showed considerable inter-observer variation in the endoscopic diagnosis of reflux oesophagitis. This was especially prevalent for Grade I oesophagitis. All endoscopies in this study was done by a single endoscopist (the author).

The endoscopy healing rate of 63.9% for the Ranitidine group compared favourably with complete healing in both Sontag *et al*'s (1987) and Johansson *et al's* (1986) studies. Sontag *et al.* (1987) had a healing rate of 56% and Johansson *et al.* a rate of 55%. The complete healing endoscopy rate of 36.4% in the Rioprostil group was disappointing. Perhaps longer treatment might have improved this figure.

Improvement in the grade of endoscopic oesophagitis occurred in 67.4% of patients in the Ranitidine group compared to an 88% improvement in Goy *et al*'s (1983) study, 63% improvement in Sontag *et al*'s (1987) study, 78% improvement in Wesdorp *et al*'s (1983) study and a 72% improvement in Lehtola *et al*'s (1986) study. These studies together with this one approximate a two-thirds improvement in the endoscopic grade of oesophagitis using Ranitidine. Rioprostil improved the grade of endoscopic oesophagitis in only 43.5%. Again, perhaps longer therapy might have improved this figure. A single patient's endoscopic oesophagitis increased in severity on Ranitidine. This may be due to the patient not taking his medication or the patient being in an in-between grade on initial endoscopic assessment.

One of the most sensitive indicators of improvement in reflux disease is histological change. Biopsies taken 5 cm from the oesophago-gastric junction prior to and at the end of the study showed both Ranitidine and Rioprostil to significantly improve the severity of the inflammation. Three patients in the Rioprostil group and one in the Ranitidine group had normal histology but definite symptoms and pH studies evidence of reflux disease. A too superficial biopsy may well account for this discrepancy. There were few studies in the literature to compare our results as most authors depended on endoscopic improvement together with symptom change to monitor improvement with treatment. However, similar significant histological improvement was obtained in the studies of Wesdorp *et al.* (1983),

Johansson *et al.* (1986), and Lehtola *et al.* (1986), using Ranitidine 150 mg bd. Biopsies in these studies were taken 1.5-5 cm above the oesophago-gastric junction and the grading of histological disease was based on the Ismail Beigi (1970) classification as was in this study. Sontag *et al*'s (1987) study, however, was at odds with the results of these studies and our study. His study showed no significant histological improvement in patients on Ranitidine compared to placebo. This discrepancy is probably due to the short duration of his therapy (6 weeks), the large number of patients who had normal histology and were entered into his study (47%), and to the high percentage of biopsy specimens (35%) that were not evaluable. Poor tissue orientation, inappropriate site and inadequate biopsy size were the reasons given for this high percentage. This is probably due to the fact that this was a multicentric trial (14 different centres).

Prostaglandins have been extensively investigated for the treatment of peptic ulcer disease and more recently as a prophylaxis against peptic ulceration in patients who are on non-steroidal anti-inflammatory drugs.

The rationale for the use of prostaglandins in peptic ulcer disease was easy to understand; prostaglandins resulted in dose dependant increases in mucus secretion (Domschke *et al.*, 1981); intragastric instillation of prostaglandins resulted in an increase in the secretion of bicarbonate ions (Johansson *et* al., 1983) and in the animal model prostaglandin infusion into the gastric artery in dogs resulted in significant and dose dependent increases in gastric mucosal blood flow (Gerkins et al., 1978). It was further demonstrated that the oral administration of synthetic analogues of PGE_1 and PGE_2 inhibited gastric acid secretion (Robert *et al.*, 1967; Wilson *et al.*, 1986), Akdamar *et al.*, 1982; Davis *et al.*, 1988). It has also been suggested that peptic ulceration may result from a failure of synthesis or deficiency

of local endogenous prostaglandins. While some studies (Alquist *et al.*, 1983) fail to show significant alterations in prostaglandin synthesis more studies have shown decreased gastric prostaglandin synthesis (Konturek, 1984; Wright *et al.*, 1982) in peptic ulcers.

Despite this overwhelming scientific evidence in favour of prostaglandins in healing peptic ulcers most clinical studies show prostaglandins to be about as effective as H_2 antagonists (Table 4.3).

TABLE 4.3 Prostaglandins and peptic ulcer.

REFERENCE	DRUG DOSE	HEALING	P VALUE
Nicholson (1985)	Misopros 200 μg Cimetidine 300 mg	62% 72%	No significance
Winters (1986)	Enpros 35 μg Cimetidine 400 mg	75% 77%	No significance
Lauritsen (1986)	Enpros 35 μg Ranitidine 150 mg	75% 89%	No significance
Walt (1987)	Enpros 70 μg Ranitidine 300 mg	52% 76%	No significance

Diarrhoea and abdominal pain were the commonest side effects encountered with the prostaglandins. Indeed, in this study four patients dropped out of the study due to diarrhoea. Thus, an advantage in favour of prostaglandins in the treatment of peptic ulcer has not emerged.

The research into the treatment of peptic ulcer disease with prostaglandins indicates that prostaglandins should certainly benefit patients with reflux oesophagitis. However, prostaglandins have not been widely investigated for reflux oesophagitis. Prostaglandins have also been shown to stimulate gastric emptying (Penston *et al.*, 1986). This is an additional important factor that should be beneficial in the treatment of reflux oesophagitis by prostaglandins.

Twenty-four hour pH monitoring was done prior to treatment and at the end of a 12 week course of treatment. Richter & Castell (1982) concluded that prolonged oesophageal pH monitoring was the most sensitive and specific test available for the diagnosis of gastro-oesophageal reflux disease. There is, however, some concern that in two studies, 23% to 29% of patients with endoscopic oesophagitis were found to have normal amounts of gastro-oesophageal reflux (Schlesinger *et al.*, 1985; Vital *et al.*, 1984). Further doubts have emerged as a result of studies in which two pH electrodes were used to monitor oesophageal pH at the same level (Murphy *et al.*, 1989). Acid exposure was recorded differently by the two electrodes in some subjects. In another study five of twenty subjects were classified differently as normal or abnormal on two consecutive study days (Johansson *et al.*, 1988).

However, there are a number of studies which show pH studies to be reproducible and specific. Weiner *et al.* (1988) found a reproducibility of 93% and 84% for pH monitoring in oesophagitis patients. Masclee *et al.* (1990) found a high specificity and sensitivity rate of 81% and 85% respectively. Using the De Meester scoring system (a positive pH test if score >17,92) a large percentage of our patients (46.4%) had negative tests despite having symptoms and endoscopic evidence of reflux oesophagitis. The explanations for this is that

many patients respond to "normal" amounts of acid in the oesophagus with symptoms and endoscopic evidence of heartburn (De Caesteeker *et al.*, 1989; Weiner *et al.*, 1988). Further, a large number of our patients had minimal endoscopic evidence of oesophagitis and the more severe the endoscopic oesophagitis the more likely the positivity of the pH tests (Masclee *et al.*, 1990).

The main practical use of pH studies is to determine if a patient is suffering from reflux disease when endoscopy proves to be normal. Masclee & Best (1990) found pathological reflux in 61% of their patients who had symptoms but no endoscopic signs of reflux. Of the eleven patients who had normal endoscopy in this study, eight had positive pH studies. Thus, the main clinical use of pH studies is to determine if the patient is pathologically refluxing despite a normal endoscopic appearance.

Our pH studies, using Rioprostil, showed no significant change in the oesophageal exposure to acid, the number of reflux episodes, and to the duration of reflux episodes before and after treatment. Rioprostil certainly promotes gastric emptying (Penston *et al.*, 1986) and inhibits gastric secretion (Demol *et al.*, 1985). Further symptoms, histologic and endoscopic improvement certainly did improve significantly using Rioprostil. Thus, the pH studies using Rioprostil appear to be at odds compared to the other results. The possibilities for this discrepancy are that the dose of the Rioprostil was not great enough to produce a significant change in the pH studies, endoscopic and symptomatic improvement occurred due to factors other than acid suppression or that the pH studies were not sensitive enough.

The sensitivity of the 24 hour pH test has recently been questioned.

The criteria by which reflux events are defined have developed empirically and have been the subject of debate (Bennett, 1987). Traditionally reflux is deemed to have occurred when oesophageal pH falls below 4 (Johnson & De Meester, 1986). Others, however, have suggested a pH threshold of 5 for scoring of reflux (Stanciu *et al.*, 1977). The magnitude of the pH drop used as an indicator of reflux has also varied among studies (Branicki *et al.*, 1984). A minimum time of 5 (Schlisinger *et al.*, 1985), 10 (Fink & McCallum, 1984), or 30 seconds (Murphy *et al.*, 1989) below the pH threshold has been adopted and some workers have also suggested that brief pH falls of less than 15 seconds represent artefact rather than reflux (Shaker *et al.*, 1992). Wyman *et al.* (1993) using pH studies concurrently with manometry showed that traditional criteria for scoring pH events substantially underestimates the number of reflux episodes. In their study up to 49% of patients with manometric evidence of reflux were missed by pH studies employing traditional criteria of reflux. In this study 10 patients who had negative studies prior to treatment changed to positive at the end of the study.

Lieberman (1988), using the H_2 blocker Cimetidine in patients with reflux disease, also found that despite endoscopic and symptomatic improvement there was no significant change in the pH studies in his patients before and at the end of treatment. He attributed this to the fact that despite pH studies reflecting the frequency and duration of reflux episodes, it fails to show the composition and volume of refluxed material, factors which are important in the pathogenesis of reflux oesophagitis. Dehn *et al.* (1990) also found no significant improvement in pH studies using high dose Cimetidine. There was also no consistent relationship between endoscopic grading and recorded acid exposure in his study.

With regard to Ranitidine, this study has shown it to significantly reduce oesophageal exposure to acid in the supine posture only. The supine posture or nocturnal acid reflux is believed to be extremely injurious to the oesophageal epithelium because of its prolonged contact with and poor clearance from the distal oesophagus (Orr *et al.*, 1984; Johnson *et al.*, 1978). Johansson *et al.* (1986) found that Ranitidine in a dose twice that used in this study diminished the total acid reflux time in his group of patients with reflux disease. Ranitidine, by acting on the parietal cell works solely by decreasing acid production. By increasing the dosage of Ranitidine there is a gradual decrease in the percentage of time that intra-oesophageal pH stays below 4 (Jansen & Lamers, 1990).

Detailed manometric evaluation to determine oesophageal motility and lower oesophageal sphincter pressures were performed at the beginning and end of the study. The mean lower oesophageal sphincter pressure prior to treatment was 12.4 mmHg for both the prostaglandin and H_2 antagonist group. This figure is at the lower limit of normal (10-26 mmHg; Benjamin *et al.*, 1983). Well over half of our patients (45/82) had lower oesophageal sphincter pressures equal to or below 10 mmHg. Despite the current thinking that reflux is due to transient relaxation of the lower oesophageal sphincter, low sphincter pressure is a common finding in patients with reflux disease.

Lower than normal sphincter pressures have also been found by other investigators in patients with reflux oesophagitis (Eckardt, 1988; Singh *et al.*, 1992; Timmer *et al.*, 1993; Baldi *et al.*, 1988). The mean lower oesophageal pressure of Singh *et al*'s patients with oesophagitis was 16.5 mmHg compared to a control group of 22.5 mmHg. Eckardt's patients had a mean of 9.8 mmHg.

Following a twelve week course of Rioprostil and Ranitidine, there was no significant change in the lower oesophageal sphincter pressure. This was a disappointing finding as it was hoped that the prostaglandin would result in an increase in the resting lower oesophageal sphincter pressure. Using 40 mg of Omeprazole daily Singh *et al.* (1992) also showed that there was no change in the sphincter pressure after healing of oesophagitis. Eckhardt (1988) using Ranitidine 150 mg bd for six weeks also had no change in pressure, while Baldi *et al.* (1988) found improvement in patients who had erosive oesophagitis when treated with Ranitidine 150 mg tds. However Baldi *et al.* only studied eight patients and found this increase only after eating. There was no improvement in the fasting resting lower oesophageal sphincter pressure.

Peristaltic contraction amplitude has been found to be lower in patients with reflux oesophagitis. Benjamin *et al.* (1982) reported a normal mean amplitude of 50-110 mmHg. Eckardt (1988) found a mean of 80 mmHg in his control group and 40 mmHg in his patients with erosive oesophagitis.

Singh *et al.* (1992) found a mean of 79 mmHg in their control group compared to 46 mmHg in their patients with oesophagitis. The mean amplitude for our patients was 44 mmHg, which is consistent with the findings of both Eckardt and Singh *et al.* There were no change in the amplitude despite treatment (Table 3.29).

The mean duration of a peristaltic contraction wave is 1.9 seconds (Benjamin *et al.*, 1982). The duration of the wave is increased in patients with oesophagitis. Our patients were found to have a mean of 3.84 seconds. Singh *et al.* (1992) found a mean of 3.1 seconds in their patients with reflux disease compared to 2.7 seconds in their control group. Eckardt (1988)

found a mean of 4.0 seconds in his group of patients with oesophagitis and Mahony *et al.* (1988) a mean duration of 4.3 seconds. Rioprostil and Ranitidine did not improve the duration of the contraction waves.

With regard to abnormal wave forms and tertiary contractions, a total of 19 patients were found to have abnormal manometric wave patterns. At the end of twelve weeks treatment eleven were unchanged, four improved, and four deteriorated. Both Rioprostil and Ranitidine failed to significantly improve tertiary contractions and abnormal wave forms. Further, there was little difference between the H_2 antagonists and the prostaglandin.

Oesophageal scintigraphy was performed in 80 patients, prior to and after treatment with Rioprostil (n=39) and Ranitidine (n=41). Measurements using liquid bolus of Tc99m pertechnetate were first described by Katzem in 1972. Bosch *et al.* (1977) used a solid gelatine bolus labelled with Tc99 showing prolonged transit in patients with obstruction. Tolin *et al.* (1970) acquired data with the patients supine to negate the effects of gravity on the bolus and used Tc99m labelled sulphur colloid. Russel *et al.* (1981) divided the oesophagus into upper, middle and lower segments and calculated the mean transit time of radionucleide in the three parts. Svedberg (1982) developed data processing of condensed images and Klein & Wald (1984) invented new computer processing that could help to predict more precisely the oesophageal motility disorder. The scintigraphic tests used in our study was developed at Ninewells Hospital, Department of Surgery, University of Dundee by Cranford *et al.* (1985). Previously, radionucleide transit studies were performed using a liquid bolus with the subjects in the supine position. The technique developed in Dundee closely reproduces the normal ingestion of solid food while in an upright posture. The test involves swallowing a 10 ml poached egg white bolus labelled with 99mTc sodium pertechnetate and

external scanning by a gamma camera. An on-line computer program allows detailed analysis by the condensed image technique and activity-time curves for the whole, the upper, middle and lower thirds of the oesophagus. The reproducibility of the test is good (co-efficient of variation of total transit of 15%). Jorgensen *et al.* (1992) using radiolabelled water found a coefficient of variation of 20-35%.

Scintigraphy has been compared to oesophageal pH monitoring.

Tolia *et al.* (1993) found scintigraphy to be more sensitive than pH monitoring in infants. Orenstein *et al.* (1992) also had similar findings. Shay *et al.* (1991) investigating nine patients with severe reflux oesophagitis found scintigraphy to be more accurate than pH studies, especially in the post-prandial period. This is probably because the refluxate during this time has a pH >4. Oesophageal scintigraphy has also been compared to manometry. As scintigraphy is much easier to perform than manometry in terms of patient comfort, time, expertise and interpretation, it was hoped that it would replace manometry. However, its predictive value of 73% (Eriksen *et al.*, 1987) of detecting abnormal motility together with the inability of scintigraphy to distinguish between particular motility disorders make it useful as a screening test only. Netscher *et al.* (1986) using a cut-off time of >15 seconds for abnormal scintigraphy found a predictive value of 96% (48/50); Blackwell *et al.* (1983) cited a value of 84% (42/50), while Mughal *et al.* (1984) were less successful with a value of only 53% (158 patients). Kaul *et al.* (1986) investigating 101 patients with gastro-oesophageal reflux found scintigraphy (86%) to be more accurate than endoscopy (68.1%) and histology (58.4%) in detecting patients with symptoms of reflux disease.

Oesophageal transit is delayed in patients with reflux oesophagitis. Cranford *et al.* (1987) using the same scintigraphic equipment and method used in this study investigated 16 normal

volunteers and 32 patients with oesophageal disease. The normal transit times obtained were 10.4 seconds (±1.6) for total time, 4.7 seconds (±1.6) proximal third, 6.5 seconds (±1.5) for middle third and 0.4 seconds (±2.5) for the distal third. All of his patients with endoscopically proven oesophagitis (n=8) had prolonged transit times apart from one who failed to swallow the entire bolus. Eriksen *et al.* (1986) also using the same scintigraphic equipment and method used in this study studied 32 patients with reflux oesophagitis and compared them to eleven controls. Oesophageal transit was significantly prolonged in 81.3% (n=26) of patients with reflux. Transit was delayed throughout the oesophagus and in each segment. Singh *et al.* (1992) found significantly prolonged oesophageal transit in all their patients with reflux oesophagitis (n=43) compared to 33 controls.

This study also shows prolonged transit in all segments of the oesophagus; upper third 22.75 seconds (normal mean 4.7 seconds ± 1.6), middle third 66.65 seconds (normal mean 6.5 seconds ± 1.5), distal third 57.37 seconds (normal mean 0.4 seconds ± 2.5), total transit 80.65 seconds (normal mean 10.4 ± 1.6). Despite treatment with both Rioprostil and Ranitidine there was no significant improvement in the transit times; upper third 25.15 seconds, middle third 48.6 seconds, lower third 37.95 seconds, total 60.55 seconds. Further, rather disappointingly, the prostaglandin failed to improve transit times and there was no statistical difference in transit between it and the H_2 antagonist.

There is continuing debate as to whether reflux oesophagitis is primarily a motility disorder or whether the motility disorder found in patients with reflux disease is a consequence of repetitive injury and inflammation caused by acid reflux. This study has shown that despite statistical improvement in endoscopic appearance, symptoms and histological appearance,

there was no statistical improvement in oesophageal manometry and transit studies indicating reflux oesophagitis to be more of a primary motility disorder.

A co-existence between hiatal hernia and reflux oesophagitis was found in 24.2% of our patients. This association was lower than that found by other investigators; Berstad *et al.* (1986) (63%) and Stene-Larsen *et al.* (1988) (68%). The majority of our patients had mild endoscopic evidence of reflux; hiatus hernia being an association but not an integral part of reflux oesophagitis as was previously thought. Clearly, as were the findings of Berstad (1986) and Stene-Larsen (1988) there were patients with severe reflux oesophagitis and no hiatus hernia and vice versa in this study.

CHAPTER 5
CONCLUSIONS AND THE FUTURE

The role of prostaglandins in reflux oesophagitis was investigated using Rioprostil, a synthetic E1 prostaglandin. Its efficacy was compared to Ranitidine, an H_2 blocker. The study provided an opportunity to examine in depth the various modalities available for the study of oesophageal function, the efficacy of the H_2 blockers themselves in the treatment of reflux disease, and importantly, whether oesophageal function improves with treatment. An attempt has been made to answer the question whether reflux disease is primarily a motor disorder or whether the motility disturbance is secondary to the inflammation caused by reflux. The association between reflux oesophagitis and hiatus hernia was also investigated.

Eight percent of patients who were on Rioprostil had to discontinue treatment due to troublesome diarrhoea. Our figure is less than the 13% found by Herting & Clay (1985) who used Misoprostil for duodenal ulcers but nonethelsss is a troublesome adverse effect of prostaglandins. The prokinetic effect of the prostaglandins accounts for this.

The symptoms of oesophagitis viz. Heartburn, regurgitation and dysphagia were improved using both Ranitidine and Rioprostil. Ranitidine was found to be superior to Rioprostil in improving the symptom of heartburn; Rioprostil was superior to Ranitidine in improving the symptoms of dysphagia and regurgitation. The known prokinetic action of the prostaglandin may account for this. There was difficulty in comparing the results of this study with others due to heartburn meaning different things to different authors. Our definition correlated with that of Goy *et al.* (1983) as did our results using Ranitidine (97% improvement compared to 82% in Goy's *et al.* study). There was no published criteria to compare the results of Rioprostil in improving symptoms of reflux disease. In comparing it to Ranitidine, it appears to be an effective agent in reducing the symptoms of reflux disease (Rioprostil reduced heartburn in 85% of patients). However, using the De Meester total symptom score

Ranitidine was found to be superior overall to Rioprostil. Acid suppression, of which Ranitidine is superior to Rioprostil (Penston *et al.*, 1986) appears to be an important factor in improving symptoms of reflux disease.

Endoscopic improvement correlated closely with symptom improvement. It is well known that reflux oesophagitis may occur in the presence of normal endoscopy (Johansson *et al.*, 1986). 13.4% of patients in this study had normal endoscopy but had symptoms and histological evidence of oesophagitis. The study showed both Rioprostil and Ranitidine to significantly improve the endoscopic grade of oesophagitis (Rioprostil in 43.5% of patients, Ranitidine in 67.4% of patients). Due to differing classifications used in grading endoscopic oesophagitis comparison with other studies had to be made with care; however, the improvement with Ranitidine endoscopically correlated with most studies (Lehtola *et al.*, 1986; Sontag *et al.*, 1987; Goy *et al.*, 1983). Complete healing of the oesophagitis occurred in 63.9% of patients in the Ranitidine group and a disappointingly low 36.4% in the Rioprostil group. Ranitidine, the more potent acid suppressing agent, must be more effective in reducing mucosal erythema and inflammation.

An accurate measure of improvement on treatment in reflux disease is obtained by histological examination which takes into account the elongation of the subepithelial papillae, the height of the epithelial basal layer and the presence of inflammatory cells in the lamina propria (Beigi *et al.*, 1970). The majority of patients in the study had minimal histological inflammation (63.4%) which correlated with the endoscopic appearance (52.4%). Both Ranitidine and Rioprostil significantly improved the histological severity of the inflammation. Neither drug was superior to the other. Similar histological improvement was found by other authors using Ranitidine (Wesdorp *et al.*, 1983; Lehtola *et al.*, 1986; Johansson *et al.*, 1986). All the

biopsies were performed by the author and the high percentage of uninterpretable specimens obtained by Sontag *et al.* (1987) (35%) and by Knuff & Benjamin (1984) (59%) were not obtained in this study due to meticulous technique. Four patients had normal histology but had symptoms and positive pH studies. This confirms the view that there is no single diagnostic investigation for reflux oesophagitis. In 5 patients histological appearance worsened on treatment. The possible cause of this may be that the patients' were in an in-between stage on initial assessment or that the medication was ineffective.

Since its description, the 24 hour pH test has attracted much enthusiasm for its reported sensitivity and specificity. Richter & Castell (1982) reported a sensitivity of 88% and a specificity of 98%. They regard this investigation as the gold standard for reflux oesophagitis. However, a more critical look at the investigation has revealed some limitations. Shaker *et al.* (1988) did 4 studies in 12 patients with endoscopic signs of oesophagitis and found a wide variation of pH indices. Wiener *et al.* (1988) showed that 95% of values could differ by a factor of 3.2 fold or less. This matters considerably if the values are borderline (pH <4 between 3 and 7%) as results on separate occasions had a 50% chance of being on the opposite sides of the boundary. This could perhaps explain the high percentage of patients (46%) who were found to have symptoms and endoscopic signs of oesophagitis but negative pH test scores in the study. A large percentage of patients who were entered into the study had normal endoscopy or minimal endoscopic oesophagitis (65%). All the patients who had moderate and severe endoscopic oesophagitis (n=28) apart from 4 were found to have positive pH studies. Thus, the findings are in agreement with that of Masclee *et al.* (1990) who found the more severe the endoscopic oesophagitis the more likely the positivity of the pH tests. PH studies were not found to be very sensitive in mild endoscopic oesophagitis. On the other

hand, of the 11 symptomatic patients with normal endoscopy, 8 had positive pH studies (72%).

Intra-oesophageal pH monitoring is a fair quantitative and objective measure of reflux with limitations and is useful clinically when the symptoms are atypical and endoscopy normal.

Intra-oesophageal pH studies performed prior to using Rioprostil and again after a 12 week course of Rioprostil showed the prostaglandin not to significantly change the oesophageal pH studies. This result is at odds with the symptomatic, endoscopic and histological improvement obtained. It suggests that factors other than acid suppression might account for the improvement obtained with the prostaglandin. These factors include improved gastric emptying (Parston *et al.*, 1986), enhanced mucus secretion (Domschke *et al.*, 1978) and increased bicarbonate ion secretion (Johansson, 1983).

This study showed Ranitidine to significantly decrease acid exposure and reflux episodes in the supine posture. The sole mode of action of Ranitidine in reflux oesophagitis is to act on the parietal cell and decrease acid production.

Oesophageal motility was studied by both manometry and radio-isotope oesophageal transit tests. The lower oesophageal sphincter was examined by manometry prior to and after treatment. The study found the mean value 12.4 mmHg to be at the lower limit of normal. It is well known that patients with severe oesophagitis have low lower oesophageal pressures (Lieberman, 1986). Currently, it is thought that transient lower oesophageal sphincter relaxations rather than the resting lower oesophageal pressure is important in the pathophysiology of reflux oesophagitis (Dent & Holloway, 1988). Thus, normal and even

elevated lower oesophageal sphincter pressure can exist in patients with reflux oesophagitis (Zielinski *et al.*, 1989).

Following a 12 week course of therapy, both Rioprostil and Ranitidine failed to improve lower oesophageal sphincter pressure. Denis *et al.* (1981), Eckhart (1988) and Wallen *et al.* (1983) also found Ranitidine to have no effect on the lower oesophageal sphincter. The E1 group of prostaglandins (Rioprostil) and their effect on the lower esophageal sphincter have not previously been studied; the F2 group has been reported to increase lower oesophageal pressure (Dilawari *et al.*, 1975) and the E2 group to have no effect on it (Schwartz *et al.*, 1985).

Diminished peristaltic amplitude implies diminished clearing and impaired motor function of the oesophagus. This study demonstrates a mean amplitude of 44 mmHg in patients with reflux oesophagitis. This is below the accepted normal amplitude of 50-110 mmHg (Benjamin *et al.*, 1982) and consistent with the findings of Eckardt (1985) and Singh *et al.* (1992). Both Ranitidine and Rioprostil failed to improve the amplitude. Schwartz *et al.* (1985) using Trimoprostil, an E2 prostaglandin, also failed to show any improvement in oesophageal peristaltic amplitude.

Similar results were obtained with the duration of the peristaltic contraction. The mean of 3.84 seconds obtained in this study (normal mean 1.9 seconds (Benjamin *et al.*, 1982)) again confirms impaired motor function in patients with oesophagitis. Confirmatory findings were found by Singh *et al.* (1992) and Eckhardt (1988). Both Ranitidine and Rioprostil failed to improve peristaltic wave duration.

Of the 66 patients that underwent manometry before and after treatment, 19 were found to have abnormal wave forms and spontaneous contractions (28%). Despite symptomatic endoscopic and histological improvement only 4 of the 19 had some improvement in their manometric tracings after treatment. Neither Rioprostil nor Ranitidine was superior. This result provides further evidence that reflux oesophagitis is primarily a motility disorder.

Oesophageal transit studies revealed prolonged transit times in all thirds of the oesophagus and in the total oesophagus in reflux sufferers. Similar results were found by Eriksen *et al.* (1986), Cranford *et al.* (1987) and Singh *et al.* (1992). Once again, despite symptomatic histological and endoscopic improvement, there was no improvement in the transit times after treatment with both Ranitidine and Rioprostil. Prolonged transit implies poor motility and prolonged oesophageal clearance. While early investigators (Tolin *et al.*, 1979) looked at scintigraphy to replace pH studies it became apparent that scintigraphy was more useful in evaluating oesophageal motility (Russel *et al.*, 1981). Indeed, oesophageal scintigraphy was found to disclose motility disorders which were undetected by standard manometric techniques (Russel *et al.*, 1981). This finding was confirmed in this study.

The ongoing controversy whether reflux oesophagitis is primarily a motility disorder or whether the motility disturbance found in patients with oesophagitis is secondary to the inflammation caused by acid reflux has been answered in this study. Despite significant endoscopic, symptomatic and histological improvement, there was no manometric evidence of improvement in motility, viz. Peristaltic wave amplitude remained diminished, wave duration remained prolonged, and in those patients who had abnormal wave forms and spontaneous contractions there was no significant improvement. Further, the lower esophageal sphincter pressure remained low. Additional evidence that healing the oesophagitis failed to improve

the motility was provided by scintigraphic studies. Total oesophageal transit and transit through the different thirds of the oesophagus remained prolonged despite healing.

This extensive study confirms the findings of the more limited studies of Singh *et al.* (1992) and Eriksen *et al.* (1989). The fact that reflux oesophagitis is due to dysmotility has important implications in the understanding and treatment of the disease. At present speculation can only be made about the nature and origin of the motor abnormalities.

The prime aim of the study was to investigate the role of prostaglandins in reflux disease. Certainly, the prostaglandin Rioprostil was found to be effective in reflux oesophagitis. It significantly reduced symptoms, significantly improved endoscopic appearance and significantly improved histological appearance. In direct comparison to Ranitidine however, it was not as effective in improving symptoms and endoscopic appearances. Further, diarrhoea was a troublesome adverse effect resulting in 4 patients unable to continue treatment. Surprisingly Rioprostil failed to significantly improve pH studies or to improve oesophageal motility as evidenced in the manometric and scintigraphic studies. It also failed to raise the lower oesophageal sphincter pressure.

The question that thus remains is how did Rioprostil improve the oesophagitis. The possibilities include the enhanced gastric emptying effect of Rioprostil (Penston *et al.*, 1986), the increased bicarbonate ion secretion by the stomach (Johasson *et al.*, 1993) or by a local mucosal effect. High local levels of prostaglandin E2 have been measured by Ottignon *et al.* (In press) in patients with reflux oesophagitis.

At present, prostaglandins are unlikely to replace acid suppressing agents such as the H_2 blockers or the proton pump inhibitors. However, as has happened in peptic ulcer therapy prostaglandins may have a role to play in non-steroidal anti-inflammatory drug- (NSAID) induced oesophagitis or the prevention of oesophageal lesions after radiotherapy.

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