Since Fyke, Code and Schlegel (1956) first demonstrated the existence of a high pressure zone at the lower end of the oesophagus, there has been increasing interest shown in this structure by anaesthetists. This area is termed the lower oesophageal sphincter (LOS) and is the major barrier preventing regurgitation of acid gastric contents into the oesophagus. This is of considerable concern to anaesthetists, as any regurgitated material may be aspirated into the lungs and produce the acid aspiration (Mendelson's) syndrome. It is of vital importance, therefore, that anaesthetists are aware of the effect of the drugs which they use on the LOS.

Regurgitation and subsequent aspiration of gastric contents remains a major cause of morbidity and mortality in clinical anaesthesia. The overall mortality from aspiration has changed little over the past 20 years in the U.K. (Edwards et al., 1956; Lunn and Mushin, 1982). In every published study on deaths attributable to anaesthesia, there have been reports of fatalities resulting from vomiting or regurgitation and subsequent aspiration (Harrison, 1978; Hovi-Viander, 1980). The occurrence of regurgitation has been estimated at 14-26% using older techniques of anaesthesia with ether, cyclopropane and uncuffed endotracheal tubes (Culver, Makel and Beecher, 1951; Berson and Adriani, 1954). Of these 7-16% had evidence of aspiration as judged by the appearance of tracer dye in the trachea at laryngoscopy and bronchoscopy. Using contemporary anaesthetic techniques and the same methodology it was shown in 1970 that the frequency of regurgitation had decreased to 7.8% and of this number, 8.6% of patients had aspirated (Blitt et al., 1970).

The lower oesophageal sphincter

Various mechanisms have been proposed in the prevention of gastro-oesophageal reflux. These include the angle with which the oesophagus meets the fundus of the stomach, acting as a flap valve. This received support from the finding in cadavers and anaesthetized man that, the more oblique the angle, the greater was the pressure required to produce reflux, yet if the angle was removed only a small gastric pressure was needed (Marchand, 1955; Greenan, 1961). The intra-abdominal length of the oesophagus may act as a flutter valve (Clark and Cuschieri, 1980), and the diaphragmatic crura may act as a pinchcock on the lower oesophagus. However, it is now generally believed that the major barrier preventing reflux is the LOS.

In man, the LOS is 2-5 cm long and moves upwards with inspiration and downwards with expiration. It extends both above and below the diaphragm (fig. 1) (Winans, 1972), and maintains a resting pressure greater than gastric. The sphincter
relaxes on swallowing to allow the passage of food into the stomach, in contrast to the body of the oesophagus which contracts in a peristaltic manner. Resting tone of the LOS, at least in the opossum, is thought to be an intrinsic property of the muscle (Goyal and Rattan, 1976).

In common with the remainder of the gastrointestinal tract, there are three muscle layers in the oesophagus—an outer longitudinal, an inner circular and the muscularis mucosae. Sphincter characteristics are thought to lie in the circular layer, because spontaneous active tension can develop in isolated strips of this layer from the gastro-oesophageal junction (in the opossum) (Christensen, Freeman and Miller, 1973). Also these strips exhibit much steeper length–tension curves compared with circular muscle from the body of the oesophagus (Christensen, Freeman and Miller, 1973) and they are more sensitive to adrenergic and cholinergic agonists (Lipshutz and Cohen, 1971).

The nerve supply to the sphincter is derived from the autonomic nervous system. The parasympathetic nerve supply is by filaments of the vagus nerve, but following vagal denervation resting sphincter pressure remains normal (Mazur et al., 1973; Temple et al., 1981). The sympathetic supply arises from T6–T10, but the precise role of these fibres is uncertain, as is the contribution to sphincter tone by the intrinsic nervous plexuses.

In addition to these nervous components there are a host of receptors present in the LOS. These receptors may be stimulated by acetylcholine, noradrenaline, histamine, 5-hydroxytryptamine, prostaglandins and the majority of the gut hormones (see review by Goyal and Rattan, 1978). As already noted, resting tone of the LOS is an intrinsic property of the muscle in that region, but this tone may be influenced by a wide variety of neural, hormonal or drug influences. Those drugs affecting the LOS which are of importance in anaesthesia are shown in Table I.

**Importance of the LOS**

The tendency to reflux is related not to LOS pressure per se, but to the barrier pressure (BrP), which is the difference between gastric and sphincter pressures. Thus patients may have a normal LOS pressure, but an increase in gastric pressure may produce reflux.

In the healthy subject there is a reflex adaptive increase in LOS pressure to an increase in intra-abdominal pressure, thus preventing reflux (fig. 1) (Lind, Warrian and Wankling, 1966; Cohen and Harris, 1971). It has been found in patients with symptoms of reflux that the adaptive response to increased intra-abdominal pressure is abnormally low. This adaptive response is decreased by atropine (Lind, Crispin and McIver, 1968) and following truncal vagotomy (Angorn et al., 1977).

**Hiatus hernia**

It is now generally agreed that the radiological appearance of a hiatus hernia is not synonymous with symptoms of reflux (Cohen and Harris, 1971). Patients with a hiatus hernia can exhibit normal LOS pressure profiles, although in these patients the LOS is always above the diaphragm. Occasionally some patients may exhibit two areas of increased pressure (fig. 2). However, patients with symptoms of reflux and a hiatus hernia exhibit lower barrier

<table>
<thead>
<tr>
<th>Increase</th>
<th>Decrease</th>
<th>No change</th>
</tr>
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<tbody>
<tr>
<td>Metoclopramide</td>
<td>Atropine</td>
<td>Propranolol</td>
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<tr>
<td>Domperidone</td>
<td>Glycopyrrolate</td>
<td>Oxprenolol</td>
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<td>Prochlorperazine</td>
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<td>Cyclizine</td>
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<td>Edrophonium</td>
<td>Ganglion blockers</td>
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<td>Neostigmine</td>
<td>Thiopentone</td>
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<td>Histamine</td>
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<td>Suxamethonium</td>
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<td>Pancuronium</td>
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<td>Metoprolol</td>
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<td>α-Adrenergic stimulants</td>
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<td>Antacids</td>
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pressures than those with an asymptomatic hiatus hernia.

There is enormous variation in LOS pressure and barrier pressures in normal individuals and, although these tend to be lower in patients with symptoms of heartburn (Lind et al., 1968) and free reflux (Haddad, 1970), there is considerable overlap between barrier pressures of normal subjects and those of patients with reflux. It is not possible, therefore, to define a barrier pressure below which all patients will have evidence of reflux, although a correlation has been found between reflux (on oesophageal pH testing) and yield barrier pressure (Haddad, 1970). Common sense, however, dictates that a reduction in barrier pressure is more likely to be associated with reflux.

**Pregnancy**

Heartburn and reflux are common features of pregnancy, and this has been related to incompetence of the LOS. It was thought that this arose from an increased intra-abdominal pressure as a result of uterine enlargement, but one would have expected a reflex adaptive increase in LOS pressure. This indeed occurs in men with tense ascites, their LOS pressures returning to normal after diuresis (Van Thiel and Stremple, 1977). In pregnancy, the LOS may be normal, but Lind and colleagues (1968) demonstrated that pregnant women with symptoms of reflux had decreased barrier pressures; 6 weeks after delivery the barrier pressures had returned to normal (fig. 3).

Serial measurements of LOS pressures and gastric secretions have been carried out during pregnancy. It has been found that LOS pressure reached its lowest point at 36 weeks gestation, but that output of basal or peak acid and basal gastric pH remained the same (Van Thiel and Wald, 1981). It was suggested that the increase in hormone concentrations either from progesterone itself or in combination with oestrogen, may be responsible. This concept gained support from the finding that LOS pressures were decreased in women taking the oestrogen–progesterone contraceptive pill (Van Thiel, Gavaler and Stremple, 1976). Further confirmation was obtained by Brock-Utne and his colleagues (1981) when they demonstrated an increase in gastric pressures in early pregnancy which did not correlate with enlargement of the uterus.

**Measurement of LOS pressure**

As the LOS is not a static structure it is detected usually by intraluminal pressure manometry. Originally, intraluminal balloons were used, but as there were sphincter pressure variations with different diameters, this method was discarded. Open-tipped water-filled catheters were used subsequently, but
were found to be inaccurate as a result of mucosal sealing of the recording orifice (Harris and Pope, 1966). In order to prevent mucosal sealing, the recording catheters were continuously infused with water (Winans and Harris, 1967). A typical arrangement would be three polyvinyl catheters taped together, each catheter having a side-hole, resulting in three recording orifices at 5, 10 and 15 cm from the tip. Originally, the recording orifices were lateral-facing, but the circularly orientated forces produced by the LOS are not equal at all points and result in radial pressure asymmetry (Kaye and Showalter, 1971). Subsequently the recording orifices were all radially orientated. However, as each catheter had its own infusion pump and pressure transducer, cumbersome plumbing was required, and measurements had to be taken with the subject in a standard position to eliminate hydrostatic pressure differences.

It is possible to overcome these problems using subminiature strain gauge pressure transducers embedded in a silastic catheter. The catheter assembly can be small (our own is only 3 mm o.d.) thereby increasing accuracy by not inducing reflex changes (fig. 4). Modern transducers require a warm-up time of only 15 min and have little variation in performance with temperature.

In order to obtain readings, subjects are fasted for at least 6 h and swallow the catheter until all transducers are in the stomach. Fifteen to twenty minutes are allowed to elapse to enable gastric hyperactivity to settle. The subject is asked to pull the tube out of the stomach, using either a station pull-through technique or a rapid pull-through technique. Sphincter pressures are identifiable easily with a rapid pull-through, as this is carried out during suspended respiration, whereas respiratory fluctuations during a station pull-through may make endpoints difficult to determine. Swallowing is not allowed during a recording because the LOS initially relaxes on swallowing, producing an abnormally low pressure and then contracts producing an abnormally high pressure.

**Pre-medication**

**Anticholinergics and anti-emetics.** Anticholinergics are not used as commonly as before for premedication, although in one study 62% of anaesthetists still routinely prescribed these drugs (Mirakhur et al., 1978). Atropine 0.6 mg administered i.v. consistently decreases LOS pressure in both animals and man (Brock-Utne et al., 1976; Laitinen et al., 1978; Cotton and Smith, 1981a). This effect is evident 3 min after i.v. injection with a significant decrease in barrier pressure at 5 min. Moreover this decrease is sustained for at least 40 min (Cotton and Smith, 1981a). Not only is barrier pressure decreased, but there is also an increase in the frequency of both free reflux and reflux produced by straining, as indicated by the presence of acid gastric contents in the lower oesophagus with pH testing (Brock-Utne et al., 1977). A similar effect was shown following the administration of hyoscine 0.4 mg i.v. (Brock-Utne et al., 1977).

Glycopyrrolate given in a dose of either 0.2 mg or 0.3 mg i.v. also decreases barrier pressure by an amount similar to that produced by atropine 0.6 mg i.v. or hyoscine 0.4 mg i.v. This effect is significant at 5 min following administration and is sustained for at least 45 min (Cotton and Smith, 1981b).

Anti-emetic drugs are used as part of premedication regimens. Metoclopramide has been shown to increase barrier pressure in both animals and man (Brock-Utne et al., 1976; Laitinen et al., 1978). Metoclopramide acts as a dopamine receptor antagonist (Baumann, McCallum and Sturdevant, 1976), dopamine causing a decrease in LOS pressure in the opossum (Rattan and Goyal, 1976). It has been suggested that a combination of atropine 0.6 mg and metoclopramide 10 mg i.v. given simultaneously produces no change in barrier pressure in humans (Brock-Utne et al., 1976). However, in anaesthetized dogs, Laitinen and his colleagues (1978) showed that, following consecutive administration of atropine and metoclopramide, the effect of whichever drug has been administered first pre-

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**Fig. 4.** Orogastric tube with transducers embedded at 5, 10 and 15 cm from the tip. This is passed into the stomach and withdrawn slowly in order to measure the LOS, gastric and oesophageal pressures. The diameter of the tube is approximately 3 mm.
dominated at the LOS. In a more detailed study in which measurements were made at 5-min intervals for 45 min, Cotton and Smith (1981a) showed in humans that the effect of atropine predominated when the two drugs were administered consecutively, irrespective of the order of administration.

Domperidone, a new anti-emetic which acts by peripheral dopamine antagonism, has also been shown to increase barrier pressure (Brock-Utne et al., 1980) and one study suggested that it antagonized the relaxant effect of atropine on the LOS (Brock-Utne, 1980). However, all these studies have utilized the i.v. route of administration, whereas 73% of anaesthetists who routinely administer an anticholinergic for premedication recommend the i.m. route (Mirakhur et al., 1978).

Fell, Cotton and Smith (1983) have shown that the i.m. administration of atropine 0.6 mg produced little effect on LOS pressure over 60 min and should not therefore increase the risk of regurgitation. However, the subsequent administration of metoclopramide 10 mg i.v. produced only a small non-significant increase of barrier pressure and therefore the use of metoclopramide in this way is unlikely to diminish the risk of regurgitation.

Of the other anti-emetics studied, both cyclizine and prochlorperazine increase LOS pressure significantly. Promethazine, however, a phenothiazine derivative with marked anticholinergic properties, decreases LOS pressure and is associated also with an increase in gastric reflux produced by stress. Droperidol, which theoretically might decrease LOS pressure as a result of α-adrenergic blocker properties, has been shown not to affect LOS pressure but to be associated with an apparent increase in free reflux of gastric contents (Brock-Utne, Rubin et al., 1978).

**Hypnotics.** The effects of diazepam on the LOS have been studied by a number of investigators. In an uncontrolled study in humans and animals, diazepam was found to decrease BrP and increase gastro-oesophageal reflux following the i.v. administration of 2.5–10 mg (Hall et al., 1975). However, in a double-blind study in volunteers, 5 or 10 mg i.v. produced no effect on BrP, whilst 20 mg produced a significant increase (Weiruch et al., 1979), measurements being made at 10-min intervals for 2 h.

Diazepam is commonly given orally before operation and, in a 10-mg dose, has been shown to produce a small but statistically significant decrease in BrP 45–75 min after ingestion (Cotton, Smith and Fell, 1981), but there was marked individual variation in respect of drowsiness and LOS tone and, furthermore, this variation did not correlate with plasma concentrations of diazepam. More recently Rubin and colleagues (1982) have shown that, 7 min after i.v. injection of diazepam 10 mg, BrP is reduced significantly. These authors also showed that, 7 min after i.v. injection of flunitrazepam 1 mg, BrP was significantly increased. The mechanism of action of benzodiazepines at the LOS is unknown, as there is no evidence for either gamma-aminobutyric acid or glycine receptors in the region of the LOS. Both of these neurotransmitters have been implicated in the central mechanisms of action of diazepam (Snyder, Enna and Young, 1977; Costa and Guidotti, 1979).

**Opiates.** Morphine 7–10 mg or pethidine 40–50 mg i.v. have been reported to decrease LOS pressure in man and Rhesus monkeys (Hall et al., 1975). Pethidine 1–3 mg kg⁻¹ when administered i.m., also produced a decrease in LOS pressure in healthy volunteers (Hey et al., 1981). Opiate receptors are found in the oesophageal myenteric plexus, although their precise function is as yet unclear. Subcutaneous injection of a synthetic analogue of met-enkephalin in human volunteers produced no change in LOS pressure, but did significantly inhibit relaxation of LOS in response to swallowing (Howard, Belsheim and Sullivan, 1982).

**Neuromuscular blockade**

**Depolarizing muscle relaxants.** It was formerly thought that the increased gastric pressure produced by suxamethonium as a result of muscle fasciculations, resulted in an increased tendency to gastro-oesophageal reflux (Anderson, 1962). However, it has been shown in anaesthetized dogs that the injection of suxamethonium 0.5 mg kg⁻¹ had no significant lasting effect on LOS pressure, but that at the depolarization phase a transient increase was noted in both the LOS and gastric pressures without any change in barrier pressure (Laitinen et al., 1978). In anaesthetized man there is not only an increase in intragastric pressure during fasciculations, but also a correspondingly greater increase in LOS pressure resulting in an increase in barrier pressure (fig. 5). There is thus no increased tendency to regurgitation in normal subjects (Smith, Dalling and Williams, 1978). The mechanism for the increase in LOS pressure is unknown, although it
FIG. 5. Pressure recordings in two subjects (top, bottom). At point T, thiopentone was given i.v. and the subject was asleep at A. At S, suxamethonium was given i.v. and F denotes onset of fasciculations. HPZ = high pressure zone (an alternative term for the LOS). Note that the increase in LOS pressure was greater than the increase in gastric pressure. (Reproduced with permission from Smith, Dalling and Williams, 1978.)
has been postulated that it could be caused by contraction of the diaphragmatic crura, by a cholinergic mimetic effect from suxamethonium itself, or by a reflex adaptive increase to an increase in gastric pressure (Smith, Dalling and Williams, 1978). It is conceivable that, if either a cholinergic mimetic effect or a reflex adaptive increase is responsible, both could be abolished by the prior administration of atropine. This would increase the tendency to regurgitation. It has been shown by Lind, Warrian and Wankling (1966) that atropine abolishes the adaptive increase in LOS pressure in response to increased intra-abdominal pressure.

Non-depolarising muscle relaxants. There has only been one study of the effects of non-depolarizing muscle relaxants on LOS pressure. Hunt, Cotton and Smith (1984) studied a group of 24 healthy, non-obese women undergoing routine gynaecological surgery. Following the administration of pancuronium 0.1 mg kg\(^{-1}\) there was a significant increase in barrier pressure at 1 min which was sustained for 5 min thereafter, remaining increased above control values, but not statistically so, for 15 min until the end of recording. They also showed in the same study that the administration of atracurium 0.6 mg kg\(^{-1}\) had no effect on LOS pressure or barrier pressure, whilst vecuronium produced a very small increase in LOS pressure.

Pancuronium is known to have anticholinergic properties (Hughes and Chappie, 1976) which account for the increase in heart rate seen with this drug. However, anticholinergic drugs cause a decrease in barrier pressure (Brock-Utne et al., 1977; Cotton and Smith, 1981a). Pancuronium also blocks the re-uptake of noradrenaline into post-ganglionic adrenergic neurones (Salt, Barnes and Conway, 1980), which accounts partly for the increase in arterial pressure encountered with the drug.

It is known that \(\alpha\)-adrenergic stimulation of the LOS results in an increase in LOS pressure (Goyal and Rattan, 1978) and it is conceivable that the increase associated with pancuronium is mediated via an effect on \(\alpha\)-adrenergic receptors in the LOS.

**Reversal of neuromuscular blockade.** Anticholinergics and anticholinesterases are used in combination to antagonize the residual effects of non-depolarizing neuromuscular blockade. Both have opposite effects on the LOS, anticholinergic agents decreasing and anticholinesterases increasing LOS pressure. Their combined effect on barrier pressure has been shown to be dose-dependent. The combination of atropine 1.2 mg with neostigmine 2.5 mg did not alter barrier pressure significantly, but if the dose of neostigmine was increased to 5 mg, there was a significant increase (Brock-Utne, Downing et al., 1978). Similarly, when neostigmine 5 mg was used with glycopyrrilate 0.6 mg, there was a significant increase in BrP, but not if neostigmine 2.5 mg had been used (Brock-Utne, 1978).

**Anaesthetic agents**

**Induction agents.** Following an induction dose of thiopentone 4 mg kg\(^{-1}\), Smith, Dalling and Williams (1978) observed a small but significant reduction in BrP after 2 min. The addition of either halothane or enflurane 2% to the inspired mixture resulted in a further decrease in BrP (Sehhati, Frey and Star, 1980), measurements being taken continuously over a period of 15 min. More recently Brock-Utne and Downing (1983) found that inhalation of 50% nitrous oxide in oxygen in normal subjects caused no significant changes in BrP, although measurements were taken at an unspecified time interval. It is difficult to reconcile these two apparently contradictory findings.

**Inhalation agents.** It has been shown that inhalation of 66% nitrous oxide in oxygen caused a highly significant decrease in BrP after 2 min. The addition of either halothane or enflurane 2% to the inspired mixture resulted in a further decrease in BrP (Sehhati, Frey and Star, 1980), measurements being taken continuously over a period of 15 min. More recently Brock-Utne and Downing (1983) found that inhalation of 50% nitrous oxide in oxygen in normal subjects caused no significant changes in BrP, although measurements were taken at an unspecified time interval. It is difficult to reconcile these two apparently contradictory findings.

**Drugs associated with anaesthesia**

**Antacids.** Antacids are commonly given to obstetric patients and patients deemed to be at risk of gastro-oesophageal reflux. Antacids have been shown to increase LOS pressure primarily by increasing intragastric pH (Castell and Levine, 1971; Higgs, Smyth and Castell, 1974). However, their use has not been associated with a decrease in mortality from aspiration pneumonitis, for which various reasons have been proposed (see review by Cotton and Smith, 1984). There is at present no evidence to suggest that any one antacid, whether of a particulate nature or not, is more effective at increasing LOS pressure. It should be remembered, however, that there is a rebound increase in production of gastric hydrogen ion following the use of antacids.

**H\(_2\)-receptor antagonists.** More recently, attention has been focused on H\(_2\)-receptor antagonists to decrease both the volume and acidity of gastric secre-
tions. It has been demonstrated in man that histamine increases LOS pressure and that this effect is mediated by H₂-receptors (Kravitz, Snape and Cohen, 1978). These authors also showed that cimetidine administered orally in doses of 200, 300 or 400 mg or by continuous infusion, did not alter LOS pressures. In another study it has been shown that ranitidine, a newer longer-acting H₂-receptor antagonist, does not alter LOS pressure when given orally or by infusion (Denis et al., 1981).

β-Blockers. Patients commonly present for surgery on long-term β-adrenoceptor blocking therapy for the treatment of hypertension and ischaemic heart disease. In addition these drugs are used frequently by the i.v. route in order to attenuate the sympathetic response to laryngoscopy and intubation (Coleman and Jordan, 1980). It has been shown that i.v. administration of 2 mg of propranolol or oxprenolol did not result in any change in barrier pressure. However, barrier pressure was significantly increased following the i.v. administration of metoprolol 2 mg (Vater et al., 1982).

Miscellaneous. Sodium nitroprusside causes a dose-dependent decrease in barrier pressure, maximal at 3 min after commencing the infusion, whereas the decrease produced by verapamil infusion is maximal 30 min after commencing the infusion (Goyal and Rattan, 1980). In man, LOS pressure is decreased by nitroglycerin (Orlando and Bozymski, 1973).

CONCLUSIONS

There is great emphasis during training of anaesthetists on manoeuvres designed to decrease the occurrence of regurgitation and subsequent aspiration. These are generally described in the technique known as "crash induction with cricoid pressure". Whilst the importance of these manoeuvres cannot be over-emphasized, henceforth greater attention should be paid to the effect of drugs and technique on the lower oesophageal sphincter—the major physiological mechanism impeding gastrooesophageal reflux.

Currently, it is known that, with the exception of metoclopramide and domperidone, all the premedication drugs used customarily have a depressant effect on LOS tone, thereby facilitating any propensity to regurgitation. Of the muscle relaxants in general use, suxamethonium is still the drug of choice for the "crash-induction" and its effects on the LOS are probably beneficial. Where suxamethonium is contraindicated and a sparing effect on the LOS is desirable, pancuronium appears to be a safe alternative.

In general, volatile general anaesthetic agents and opiates decrease LOS tone, but there are insufficient data currently available on which to base rational preferences in the patient in whom the trachea is not protected by a cuffed tube.

Although the anticholinergic drugs are powerful depressants of LOS tone, causing a reduction in barrier pressure, it appears that, fortuitously, the combination of neostigmine 2.5 mg and atropine 1.2 mg has a net negative effect on the LOS. Nonetheless, in the period after operation, patients may still be under the influence of opiates or volatile anaesthetic agents and therefore the risk of gastro-oesophageal reflux is increased in comparison with the healthy non-medicated subject.

REFERENCES


