EVALUATION OF THE COMBINED EFFECTS OF GLYCOPYRROLATE AND NEOSTIGMINE ON THE LOWER OESOPHAGEAL SPHINCTER

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The intrinsic tone of the lower oesophageal sphincter (LOS) represents the major barrier to gastro-oesophageal reflux. The barrier pressure (BrP) represents the pressure gradient which opposes reflux and it is calculated by subtracting gastric pressure (GP) from LOS pressure. In view of the importance of regurgitation to the anaesthetist, there have been many investigations of the effects of anaesthetic drugs and techniques on BrP in recent years.

On a previous occasion, we examined the effects of a combination of atropine 1.2 mg and neostigmine 2.5 mg on BrP and demonstrated that a significant reduction occurred (Turner and Smith, 1985). This was evident soon after the administration of the drugs. Although this is a potentially deleterious effect, it is probably not important clinically because it was short-lived. There has been increasing use of glycopyrrolate instead of atropine and, because of its relatively long duration of action, we have investigated the effects of glycopyrrolate 0.5 mg and neostigmine 2.5 mg (Klingenmaier et al., 1972) under the same circumstances as in our previous study.

PATIENTS AND METHODS

Twelve healthy patients undergoing elective intra-abdominal gynaecological surgery gave informed consent to take part in this study, which was approved by the District Ethical Committee. The subjects were free from gastrointestinal, respiratory or cardiovascular disease, were not receiving any medication and, where appropriate, had refrained from smoking for the 8 h before the induction of anaesthesia.

The same anaesthetic technique was used as in our previous study (Turner and Smith, 1985): premedication with diazepam 0.2 mg kg\(^{-1}\) by mouth 2 h before operation, induction with thiopentone 4 mg kg\(^{-1}\), and pancuronium 0.1 mg kg\(^{-1}\) to facilitate tracheal intubation and artificial ventilation (minute ventilation of 100 ml kg\(^{-1}\)). Anaesthesia was maintained with 70% nitrous oxide and 0–1% enflurane in oxygen with morphine sulphate for analgesia.

The oesophageal manometry tube (Gaeltec Ltd) was connected via a preamplifier to a multichannel chart recorder (Linear Recorder Mk III). In brief, it contains three small pressure transducers 5, 10 and 15 cm from its tip, is calibrated in a water column before use and again at the end of the study, and has insignificant calibration or baseline drift over periods exceeding...
90 min and with temperature variations of 1–2 °C. A full description of the apparatus and method of measurement by “pull through” manoeuvre may be found in previous publications from this department (Turner and Smith, 1985; Cotton and Smith, 1981; Cotton and Smith, 1984). Pull through manoeuvres in which all three transducers pass from stomach through the lower oesophageal sphincter to oesophagus are made at end expiration and show sequential measurements of these pressures on the channels from each transducer in turn. Artefacts such as coughs and swallows can be distinguished as they are recorded from each transducer simultaneously. The barrier pressure is calculated from the measurements of gastric pressure and lower oesophageal sphincter pressure. In the present study three control measurements were taken during stable anaesthesia before the antagonism of residual neuromuscular blockade. After the administration of neostigmine 2.5 mg and glycopyrrolate 0.5 mg, measurements were taken every 1 min for 20 min, during which time anaesthesia was maintained with 70% nitrous oxide and 0.2% enflurane in oxygen to prevent the patient straining or coughing.

All the results were assessed statistically using analysis of variance followed by Student’s t test for paired data, comparing each minute with control. A comparison with those of the previous study was made to assess whether the atropine–neostigmine sequence or the glycopyrrolate–neostigmine sequence had the more marked effect on BrP.

RESULTS

After the administration of glycopyrrolate and neostigmine, all except one of the patients showed a biphasic response in BrP over the period of 20 min. After an inconsistent and very brief decrease, there was a sharp increase and then a prolonged decrease. The pressure changes did not occur at exactly the same time in each patient, but there was a statistically significant (P < 0.05) reduction in BrP by 8 min which was sustained throughout the period of study. From a control value of 27.2 cm H₂O ± 3.4 (SEM) BrP decreased to 18.8 cm H₂O ± 1.3 at 8 min and remained low, reaching 16.1 cm H₂O ± 1.3 at 20 min—the end of the study period (fig. 1). These results contrast with those of the previous study in which, after the administration of atropine 1.2 mg and neostigmine 2.5 mg, the potentially deleterious effect of the atropine was rapidly negated by the neostigmine such that by 3 min the net effect on LOSP and BrP was negligible. Table I shows a comparison of the lowest values of BrP reached in the two studies, this value as a percentage of control BrP, and the time at which this occurred.

DISCUSSION

It is generally believed that the resting tone in the lower oesophageal sphincter is the major barrier to gastro-oesophageal reflux (Cohen and Lipshtutz, 1971). The variable which is important in preventing reflux is not the LOS tone itself, but the pressure difference between the LOS and the stomach and this is referred to as the barrier pressure. It is not possible to define a barrier pressure below which all patients exhibit gastro-oesophageal reflux, although a correlation has been demonstrated between reflux (utilizing
oesophageal pH testing) and yield barrier pressure (Haddad, 1970). It is, therefore, suggested that a reduction in barrier pressure is likely to be associated with an increased tendency to regurgitation (Cotton and Smith, 1984). This has been confirmed by a study of the effect of hyoscine and atropine on the lower oesophageal sphincter in volunteers. Brock-Utne and colleagues (1977) demonstrated, in 16 healthy volunteers devoid of gastrointestinal disease, that both atropine 0.6 mg and hyoscine 0.4 mg, produced decreases in barrier pressure of the order of 10 cm H₂O, which led to reflux being demonstrable on straining in 25% of the subjects. This suggests that a relatively moderate reduction in barrier pressure may be associated with an increased tendency to reflux.

Normally, there is an adaptive reflex increase in LOS pressure to an increase in intra-abdominal pressure, thus preventing reflux (Lind, Warrian and Wankling, 1966). It has been shown that this adaptive response is diminished following the administration of atropine (Lind, Crispin and McIver, 1968), and it is also decreased in pregnant women at term who have symptoms of reflux (Lind et al., 1968).

Thus, the effects on the LOS, of drug and drug combinations used during general anaesthesia, may be important, particularly if these effects have a long duration of action. It has been reported previously (Turner and Smith, 1985) that antagonism of neuromuscular blockade with atropine and neostigmine did cause a significant decrease in barrier pressure, but this effect was transient.

In the present study, a combination of glycopyrrolate 0.5 mg and neostigmine 2.5 mg was shown to cause a significant reduction in barrier pressure of 50% (of the order of 10 cm H₂O) which, by analogy with the study of Brock-Utne and colleagues (1977) might be expected to be associated with reflux on straining in some patients. Furthermore, the significant reduction in barrier pressure lasted for as long as 20 min in some patients. The deleterious effects of the combination of neostigmine and glycopyrrolate on the LOS may, therefore, still be present once the trachea has been extubated, and the patient returned to the recovery area or the general surgical ward.

A control group was not included in the present study since previous studies from this Department have demonstrated that, over the duration of this study, and with the techniques used, there is no significant variation in barrier pressure with time (Cotton, Smith and Fell, 1981). Furthermore, our previous study on the effect of atropine and neostigmine on the lower oesophageal sphincter (Turner and Smith, 1985) showed that barrier pressure demonstrated only a transient decrease in a group of patients undergoing the same type of surgery under identical anaesthetic conditions.

The results suggest that when glycopyrrolate and neostigmine are given simultaneously in the standard clinical doses, the patient may be at increased risk of regurgitation from decreases in barrier pressure. This drug combination should probably be avoided in situations where regurgitation is likely, and our previous study suggests that the combination of atropine and neostigmine is preferable.

REFERENCES


