SINGLE AND COMBINED EFFECTS OF ATROPINE AND METOCLOPRAMIDE ON THE LOWER OESOPHAGEAL SPHINCTER PRESSURE

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SUMMARY

The effects of atropine and metoclopramide on the lower oesophageal sphincter pressure (LOSP) were studied in 12 healthy volunteers using oesophageal pressure transducers. Atropine decreased LOSP significantly at 5 min after i.v. injection (P < 0.005) and this change was sustained for 60 min. Metoclopramide increased LOSP significantly at 3 min after administration i.v. (P < 0.05) and this change was sustained for 40 min. Following consecutive administration of the drugs, the effects of atropine predominated.

At the lower end of the oesophagus is a region of increased intraluminal pressure termed the lower oesophageal sphincter (LOS) or high pressure zone (HPZ). Although this region is not anatomically distinct, its position may be identified and tone quantified by oesophageal manometry. The lower oesophageal sphincter is thought to be an important mechanism in the prevention of reflux of gastric contents into the oesophagus and therefore there has been considerable interest recently in changes in LOS magnitude produced by drugs encountered during anaesthetic practice.

It is generally assumed that tendency to regurgitation may be related to the barrier pressure (BP), which is the difference in pressure between the gastric and the high pressure zone. Although all previous studies suggest that atropine decreases and metoclopramide increases BP (table I), only one study of the simultaneous administration of atropine and metoclopramide showed that there was no change in LOS pressure (Brock-Utne et al., 1976). In addition, it has been shown in anaesthetized dogs that the random consecutive administration of atropine and metoclopramide with a 5-min interval produced no alteration in BP from the change produced by the first drug (Laitinen et al., 1978). However, in all these studies there was no indication of the timing of the single measurement.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Drug</th>
<th>BP</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1968</td>
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<td>A</td>
<td>Decrease</td>
<td>After at least 5 min</td>
</tr>
<tr>
<td>1976</td>
<td>Brock-Utne and others</td>
<td>A</td>
<td>Decrease</td>
<td>None made</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>Increase</td>
<td>None made</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A + M</td>
<td>No change</td>
<td>None made</td>
</tr>
<tr>
<td>1977</td>
<td>Brock-Utne and others</td>
<td>A</td>
<td>Decrease</td>
<td>None made</td>
</tr>
<tr>
<td>1978</td>
<td>Laitinen and others (anaesthetized dogs)</td>
<td>A</td>
<td>Decrease</td>
<td>None made</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>Increase</td>
<td>None made</td>
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<tr>
<td></td>
<td></td>
<td>Consecutive A + M</td>
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<td></td>
<td></td>
<td>Consecutive M + A</td>
<td>No decrease following initial increase</td>
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</tbody>
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which was made following the i.v. injections of the drugs and no assessment of the time-course or duration of effects. The purpose of this study was to define the onset and duration of action of atropine and metoclopramide following both their single and consecutive administrations in man.

**METHODS**

Twelve healthy volunteers (ages 21–38 yr) with no history of gastrointestinal, respiratory or cardiovascular disease, and not receiving any drug therapy, gave informed consent to take part in this study. Eight subjects were male and, of the total, five were smokers. All subjects had fasted and, where relevant, refrained from smoking for at least 6 h before swallowing a silastic nasogastric tube (3 mm o.d.) into which were embedded three subminiature strain gauge pressure transducers situated laterally at 5, 10 and 15 cm from the distal tip (Gaeltec Ltd). This was connected via a preamplifier to a chart recorder (Linearcorder Mk III). Each transducer was calibrated by immersion in a column of water at 37 °C. Preliminary assessment of the performance of the transducers revealed negligible drift in calibration with a 2°C variation in temperature and an insignificant drift in calibration or zero baseline over a period of 60–90 min.

The tube was swallowed orally until all the transducers were in the stomach and a period of 15–20 min was allowed to elapse to enable gastric hyperactivity to diminish. Control measurements of gastric (GP) and HPZ pressures were then made by withdrawal of the tube from the stomach in increments of 0.5 cm with pauses of a few seconds, through the HPZ until all the transducers were in the oesophagus. The proximal transducer enabled pressure changes produced by swallowing to be recognized from the oesophageal tracing as described previously (Smith, Dalling and Williams, 1978). When swallowing occurred, all measurement was discarded and the pull-through manoeuvre was repeated. All measurements were related to the end-expiratory point.

Each volunteer swallowed the tube on three separate occasions. On the first occasion, the subject received atropine 0.6 mg i.v. or meto-
clopramide 10 mg i.v. The order of administration was randomized between subjects. On the second occasion each received the second drug. On the third occasion six of the volunteers received atropine 0.6 mg followed 10 min later by metoclopramide 10 mg; the other six volunteers received the drugs in reverse order. Measurements were made at 3 min, 5 min and then 5-min intervals following the i.v. injections of the drugs until the end of recording at 60 min for atropine, 40 min for metoclopramide and 50 min for the consecutive administration study. At the end of recording, the tube was removed and the zero baseline and calibration were re-assessed.

All results were analysed using Student's *t* tests for paired data.

**RESULTS**

Metoclopramide produced an increase in BP from $16.1 \pm 1.4$ (mean ± SEM) to a maximum at 5 min after injection of $24.8 \pm 2.3$ cm H$_2$O ($P<0.005$). Thereafter barrier pressure remained increased significantly until the end of recording at 40 min post-injection (fig. 1). It may be seen from figure 1 that significant increases in BP and HPZ pressure were apparent 3 min after injection.

In contrast, atropine decreased BP from $18.8 \pm 1.4$ cm H$_2$O to $13.5 \pm 1.4$ cm H$_2$O ($P<0.01$) and the pressure remained decreased significantly until the end of recording at 60 min. However, at 55 and 60 min this decrease in BP resulted from a significant increase in GP ($P<0.005$) rather than a decrease in HPZ pressure. Again, the effect of atropine was evident when the first measurement was made 3 min after injection (fig. 2).

When both drugs were given consecutively, BP decreased significantly from $16.9 \pm 2.3$ cm H$_2$O to $10.5 \pm 1.5$ cm H$_2$O ($P<0.05$) (in those who received atropine first). However, following the injection of metoclopramide, BP did not increase significantly above the values to which it had decreased following atropine (fig. 3). These changes were sustained until the end of recording at 50 min, apart from the measurement at 35 min, when BP approximated to control values.

For the subjects who received metoclopramide first (fig. 4), BP increased from $21.7 \pm 2.8$ cm H$_2$O to $27 \pm 1.8$ cm H$_2$O. However, following the in-

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![Graph](https://via.placeholder.com/150)

**Fig. 2.** Effect of atropine 0.6 mg (ATR) i.v. on gastric (GP), barrier (BP) and lower oesophageal sphincter (HPZ) pressures in healthy volunteers (mean ± SEM, *n* = 12).
FIG. 3. Effect of atropine 0.6 mg (ATR) i.v. followed 40 min later by metoclopramide (MET) 10 mg i.v. on barrier pressure (HPZ minus gastric pressure) (mean ± SEM. n = 6).

FIG. 4. Effect of metoclopramide (MET) 10 mg i.v. followed 10 min later by atropine (ATR) 0.6 mg i.v. on barrier pressure (HPZ minus gastric pressure) (mean ± SEM. n = 6).
jection of atropine, BP decreased to 16.3 ± 2.9 cm H₂O, a value not only significantly different from that to which it had increased \((P < 0.025)\), but also less than control \((P < 0.05)\). These changes were sustained until the end of recording at 50 min (fig. 4).

**DISCUSSION**

This study confirms previous observations that, when given independently, atropine decreases and metoclopramide increases BP (Skinner and Camp, 1968; Brock-Utne et al., 1976, 1977; Laitinen et al., 1978). Although the extent of the decrease following atropine is comparable to that noted in previous studies, it is not possible to make strict comparisons. It is well recognized that different types of measuring system record different pressures in the LOS region.

We noted that following atropine, BP decreased significantly by 3 min after injection and this decrease persisted for 60 min. However, inspection of figure 2 reveals that there appeared to be a trend for both HPZ and gastric pressure to increase by a small amount towards the end of recording and therefore it is not possible to state confidently that the duration of action of atropine on the sphincter persists for as long as 60 min. Metoclopramide has been shown to have a duration of action on the gut of 20–40 min following i.v. injection (Robinson, 1973) and our results suggest a similar duration of effect on the LOS.

It has been shown in the opossum that the action of metoclopramide on LOS is not antagonized by anticholinergic agents (Cohen and De Marino, 1976); similar findings have been reported in anaesthetized dogs (Laitinen et al., 1978). However, the results of the present study in man demonstrate that the action of metoclopramide is obscured by that of atropine when these drugs are given in clinical doses and that the effect persists for at least 40 min.

Metoclopramide acts directly on the LOS muscle at a site which is different from that of the cholinergic receptor and there is a suggestion that the drug may act as a dopamine receptor antagonist (Bauman, McCallum and Sturdevant, 1976). Dopamine is known to decrease LOS pressure in the opossum (Rattan and Goyal, 1976) and thus blockade of these receptors would theoretically lead to an increase in LOS pressure which should not be antagonized or potentiated by effects on cholinergic receptors. Although we have demonstrated in this study that atropine 0.6 mg and metoclopramide 10 mg produce changes of approximately the same magnitude, the effects of atropine appear to predominate. However, because there are many factors influencing the tone of LOS, including cholinergic, adrenergic and reflex mechanisms, it is not possible to speculate upon the mechanism of action of metoclopramide on the LOS in man.

Gastro-oesophageal reflux depends to a large extent on the barrier pressure between the stomach and the high pressure zone at the lower end of the oesophagus (Haddad, 1970; Cohen and Harris, 1971). It is therefore important for anaesthetists to consider the effects on barrier pressure of the drugs used in clinical practice. Such considerations should include not only peak effects, but also rate of onset and duration of action.

Silent regurgitation has been reported in 7.8% of a group of patients for various general surgical procedures and of those, 8.6% had evidence of pulmonary aspiration (Blitt et al., 1970). In obstetric anaesthetic practice, the frequency of maternal deaths attributed to pulmonary aspiration has remained unchanged in the last two triennial reports. It has been suggested that metoclopramide be used as a means of reducing the frequency of regurgitation (Brock-Utne et al., 1976); however, our results suggest that atropine exerts a predominant effect over metoclopramide on the LOS pressure. Any benefit of an increase in BP produced by metoclopramide would be abolished by the consecutive use of atropine.

**REFERENCES**


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**EINZELNE UND KOMBINIERTE EFFEKTE VON ATROPIN AUF DEN UNTEREN SPEISEROHREN-SCHLIESSMUSKELDRUCK**

ZUSAMMENFASSUNG
Die Wirkungen von Atropin und Metoclopramid auf den unteren Speiseröhren-Schließmuskeldruck (LOSP) wurden an 12 gesunden Freiwilligen mittels Ösophageal-Druckwandlern untersucht. Atropin senkte den LOSP wesentlich—5 min nach intravenöser Verabreichung \((P<0,005)\), und dieser Wert blieb 60 min lang erhalten. Metoclopramid erhöhte den LOSP wesentlich—3 min nach intravenöser Verabreichung \((P<0,05)\), und dieser Wert blieb 40 min lang erhalten. Nach konsekutiver Verabreichung beider Drogen blieb die Wirkung von Atropin vorherrschend.

**EFFETS INDIVIDUELS ET COMBINES DE L'ATROPINE ET DE LA METOCLOPRAMIDE SUR LA PRESSION DU SPHINCTER OESOPHAGIEN INFERIEUR**

**RESUME**
Chez 12 volontaires en bonne santé, on a étudié les effets de l'atropine et de la metoclopramide sur la pression du sphincter oesophagien inférieur (LOSP) au moyen de transducteurs de pression oesophagienne. L'atropine a fait diminuer la LOSP de manière significative 5 min après l'injection i.v. \((P<0,005)\) et cette modification s'est maintenue pendant 60 min. La metoclopramide a fait augmenter la LOSP de manière significative 3 min après l'administration i.v. \((P<0,05)\) et cette modification s'est maintenue pendant 40 min. Après une administration consécutive de ces substances, les effets de l'atropine furent prédominants.

**EFFECOS INDIVIDUALES Y COMBINADOS DE LA ATROPIA Y DE LA METOCLOPRAMIDA EN LA PRESION DEL ESFINTER ESOFAGICO INFERIOR**

**SUMARIO**
Se estudiaron los efectos de la atropina y de la metoclopramida en la presión del esfínter esofágico inferior (LOSP) en 12 voluntarias sanas por medio de un transductor de presión esofágica. La atropina redujo la LOSP de manera significante 5 min después de la inyección i.v. \((P<0,005)\) y este cambio se mantuvo durante 60 min. La metoclopramida aumentó la LOSP de manera significante 3 min después de la administración i.v. \((P<0,05)\) y este cambio se mantuvo durante 40 min. Luego de la administración consecutiva de estas substancias, los efectos de la atropina predominaron.