Effect of metoclopramide given before atropine sulphate on lower oesophageal sphincter tone

J. G. BROCK-UTNE, G. E. DIMOPOULOS, J. W. DOWNING, M. G. MOSHAL

Summary
The effects on lower oesophageal sphincter (LOS) tone of sequential intravenous injections of metoclopramide 10 mg/atropine 0.6 mg and atropine 0.6 mg/metoclopramide 10 mg, given randomly on separate occasions to 8 healthy volunteers, were studied.

The administration of metoclopramide increased mean LOS pressure by 13.6 cm H₂O (P < 0.001). Subsequent injection of atropine failed to lower LOS pressure significantly, LOS pressure being sustained at a mean of 11.2 cm H₂O above basal control levels (P < 0.01). In contrast, injection of atropine at a later date in the same subjects lowered the average LOS pressure by 10.5 cm H₂O (P < 0.001), and subsequent intravenous injections of metoclopramide restored LOS pressure to basal levels.

The results of this study suggest that metoclopramide should be given prior to atropine before induction of general anaesthesia to counteract the deleterious effects of atropine on LOS tone, thereby helping to reduce the chances of regurgitation and pulmonary aspiration of acid gastric contents.

Subjects and methods
Oesophageal manometric studies were performed on 8 healthy volunteers, all of whom gave their informed consent. The study was approved by the Ethics and Standards Committee of the Faculty of Medicine, University of Natal. Any previous history of upper gastro-intestinal surgery or disease precluded entry to the study. Volunteers were studied on two separate occasions after a fast of at least 10 hours before the investigation. At the first study session, basal gastric, LOS and oesophageal pressures were recorded at rest. Thereafter, metoclopramide 10 mg was given intravenously and oesophageal motility studies were repeated 5 minutes later. Subsequently, atropine 0.6 mg was administered intravenously and further pressure recordings were made, again 5 minutes after the injection.

Approximately 2-3 months later the same subjects were studied again in a similar manner, but with the drugs being given in the reverse order, atropine preceding metoclopramide. The selection of 7 minutes as the delayed time before pressure recordings were made stems from our previous experience with these drugs.3 The manometric technique employed in this study was identical to that previously described.9

Three polyethylene tubes bonded together at the distal end were swallowed by the volunteer. These catheters, continuously flushed by a Harvard constant infusion pump at a rate of 0.19 ml/min, were attached to three separate transducers. The latter were calibrated between 0 and 80 cm H₂O before and after each study, using a water manometer.

The transducers were positioned at approximately the level of the lower oesophagus (mid-axillary line) to eliminate the effects of hydrostatic pressure. A motility catheter was passed orally until all the recording orifices lay in the stomach. The tube was slowly withdrawn, 0.5 cm at a time, until the pressure recordings and their alterations in response to swallowing indicated that all three orifices now lay within the oesophagus above the LOS.

The tracings obtained represent pressure changes in all three tubes. Hence three pressure values (gastric, sphincter and oesophageal) were obtained each time the catheter was pulled free from the stomach into the oesophagus. Actual pressures were measured from the baseline (zero pressure) to the midpoint between maximal end-inspiratory and end-expiratory points of the respiratory fluctuations shown on the tracings. The mean gastric pressure (GP), LOS pressure (LOSP) and oesophageal pressure (OP) were measured for each subject before and after receiving the drugs. The difference between LOSP and GP is termed the barrier pressure (BP). All pressures are expressed as cm H₂O above atmospheric pressure. Only tracings which were without interference from movement, swallowing and gross respiratory excursions were evaluated.

All pressure tracings were measured by an independent observer (G. E. D.). Statistical analyses were performed using Student's t test for paired data on a Hewlett-Packard desk-top calculator (No. 9815A). A P value of < 0.05 was regarded as significant.
Results

The average age of the volunteers was 32.8 years (SEM 3.7 years) and their mean body mass was 70.1 kg (SEM 1.5 kg). The mean pressures recorded at the first session under resting control conditions were GP 20.9 cm H2O, LOSP 57.4 cm H2O and OP 1.6 cm H2O. The average calculated BrP was therefore 36.5 cm H2O. Following metoclopramide administration highly significant increases in both the LOSP and BrP — 71 cm H2O and 48.9 cm H2O ($P < 0.001$) respectively — were observed. Subsequent atropine administration caused little change in LOSP and BrP, making these pressures significantly ($P < 0.01$) higher than basal levels.

The mean control basal resting pressures recorded on the second occasion were GP 20.2 cm H2O LOSP 51.3 cm H2O and OP 2.5 cm H2O. The average calculated BrP was 31.1 cm H2O. After administration of atropine, significant decreases in mean LOSP and BrP — 40.8 cm H2O ($P < 0.001$) and 22.7 cm H2O ($P < 0.001$) — were seen. Later administration of metoclopramide increased both the LOSP and BrP basal levels.

The average gastric pressure decreased significantly ($P < 0.05$) after atropine administration and returned to the basal level after the subject had received metoclopramide. Oesophageal pressures were unchanged throughout this study period, except for a slight rise after metoclopramide ($P < 0.005$). Results are tabulated in Table I.

Discussion

The LOS is a specialized structure physiologically different from the body of the oesophagus, and presents the main barrier to gastro-oesophageal reflux.

The amount of gastric contents entering the oesophagus depends on the competence of the anti-reflux mechanism. Oesophageal manometric measurements have shown that the LOS becomes incompetent at barrier pressures below 13 cm H2O.

Atropine has been shown to reduce and bethanecol to increase LOS tone, with a marked increase in the incidence of gastro-oesophageal reflux after atropine and a significant reduction in gastric reflux with bethanecol. The detrimental effect of atropine on LOS tone was later confirmed by other workers in both non-pregnant and pregnant humans. Recently Laitinen et al. have shown in dogs that metoclopramide increased LOSP significantly and that subsequent atropine administration failed to influence the LOS tone. The present study in man confirms their findings. Laitinen and his co-workers showed that when atropine was given before metoclopramide the latter drug failed to elevate LOSP previously reduced by atropine. However, in our study metoclopramide after atropine injection increased LOSP to near basal levels. The reason for this discrepancy could be the timing of the pressure measurements after the second drug administration. The Laitinen study and the present study show that the order of injection of atropine and metoclopramide before induction of anaesthesia may be important to the anaesthetist. This is especially so since we have previously advocated that metoclopramide and atropine be given simultaneously before emergency surgery and caesarean section.

The reasons for using atropine — especially before anaesthesia for caesarean section — have been discussed. We are reluctant to change this practice, especially in view of the most recent confidential report on maternal mortality from the UK in which 2 women were deemed to have died because atropine was excluded from the pre-anaesthetic sequence.

Metoclopramide has previously been recommended for use in premedication for anaesthesia because it is an anti-emetic and speeds up gastric emptying. The mechanism of action of metoclopramide is poorly understood. There are three major current hypotheses about its mechanism of action on smooth muscle: enhancement of cholinergic excitatory processes at the post-ganglionic myoneural junction, inhibition of non-cholinergic, non-adrenergic motor inhibitory neurons, and direct action on the muscle. The results presented here suggest that since the most likely action of atropine on LOS is to block the effect of acetylcholine at the post-ganglionic myoneural junction, metoclopramide could act at this site. A competitive drug receptor interaction would seem to occur. Of relevance here is the work of Ostick and Hey, who showed that following administration of pethidine LOS tone was reduced, but that subsequent metoclopramide injection increased the LOSP significantly.

In this and previous studies metoclopramide has been shown to be relatively free of undesirable side-effects in conscious adults. Recently, some doubt about the drug’s effects on cardiovascular stability during anaesthesia has been expressed. However, Thorburn and Sowton found that the drug caused minimal cardiovascular changes in 21 conscious patients undergoing cardiac catheterization.

It is therefore concluded that metoclopramide should be given prior to atropine before induction of general anaesthesia to counteract the deleterious effects of atropine on LOS tone and reduce the chances of regurgitation and pulmonary aspiration of acid gastric contents.

Our thanks are due to Mr N. Naiker for technical help and to Mrs G. Swart for secretarial assistance.

<table>
<thead>
<tr>
<th>TABLE I. STOMACH, SPHINCTER, OESOPHAGEAL AND BARRIER Pressures (cm H2O) (Mean ± SEM) Before and After Metoclopramide and Subsequent Atropine Injection and at a Later Date Atropine and Subsequent Metoclopramide Administration</th>
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<tbody>
<tr>
<td><strong>First study</strong>&lt;sup&gt;†&lt;/sup&gt;</td>
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<tr>
<td><strong>Gastric pressure</strong></td>
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<tr>
<td>20.9 ± 0.8</td>
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<tr>
<td><strong>Sphincter pressure</strong></td>
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<tr>
<td>20.9 ± 0.8</td>
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<tr>
<td>57.4 ± 4.5</td>
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<tr>
<td>51.3 ± 4.1</td>
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<td>1.6 ± 0.4</td>
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<td>2.5 ± 0.6</td>
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<td>36.5 ± 4.9</td>
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<td>31.1 ± 4.1</td>
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</table>

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

† There is a significant difference between basal and atropine levels in the first study. Both the sphincter and barrier pressures are higher than basal levels ($P < 0.01$).

‡ There is no significant difference between basal and metoclopramide levels in the second study.
REFERENCES


Review Article
Some metabolic aspects of arthritis
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Summary

Arthritis commonly accompanies clinical disturbances of metabolism, while diseases which are primarily articular may cause major general metabolic abnormalities. The relationship between diet, nutrition and joint disease is complex and varies from simple mechanical factors (as in obesity) to complex metabolic processes. Current knowledge of these processes is extensive in some areas, such as in gout and hyperuricaemia, whereas in others, such as the arthropathy encountered after intestinal bypass surgery, it is very scant indeed.

Joint disorders in hyperlipoproteinaemia and diabetes mellitus are varied and the pathogenesis of these articular problems is as yet ill understood. In view of the frequency with which these metabolic problems occur, these disorders offer no opportunities for the clinical study of the processes involved in joint inflammation and damage. In contrast, metabolic abnormalities such as hypergastrinaemia and elevated ionized calcium in rheumatoid arthritis are worthy of study, as they may offer clues to the underlying aetiology of the joint disease. This latter abnormality is suggestive of hyperparathyroidism, a condition which may present with polyarthritis and in which joint changes may be severe, although they are usually obscured by the more obvious bony problems in this disease. An illustrative historical vignette is included.


Obesity

It is still far from clear why some individuals can eat as much as they desire and remain lean, whereas others who are sparing in their caloric intake become obese, and at times grossly so. Exhaustive studies of the basal metabolic rate, and of energy expenditure from physical activity, and of the thermic effect of food (the immediate energy expenditure required to digest, absorb and process a meal), have failed to identify a specific defect. Apart from the external situation of total or near fasting there is growing evidence that obesity is as much, or even more, influenced by as yet undefined metabolic defects as by caloric intake. One probable cause which has recently been investigated has been the functioning of brown fat, a heat-producing tissue. Since obesity is perhaps the commonest 'metabolic' disease in the Western world, it is perhaps appropriate to first discuss arthritis associated with this condition.

The pattern of joint involvement of osteo-arthritis in obese subjects has been studied by Lawrence. All joints from the waist...