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Influence of morphine on the distal oesophagus and the lower oesophageal sphincter – a manometric study

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SUMMARY Basal pressure and relaxation of the lower oesophageal sphincter (LOS) as well as amplitude, duration and propagation velocity of peristaltic waves in the distal third of oesophagus were measured in 15 healthy adults (nine men and six women). A highly standardised technique was used employing manometric equipment including a low-compliance pneumohydraulic infusion system and a triple lumen recording catheter. After establishment of baseline manometry values the catheter was positioned with its distal orifice in the lower oesophageal sphincter. In 10 subjects 0·2 mg/kg body weight of morphine sulphate was then injected subcutaneously. In five others equal volume of saline was given. The manometric data were analysed blindly. Repeated manometric evaluations were carried out 15, 30, 45, 60, and 75 minutes after the injection. Morphine increased slightly LOS-pressure and significantly ($p<0·001$) decreased LOS-relaxation, the maximal effect occurring 30 minutes after the injection. Amplitude of peristaltic waves increased slightly but insignificantly, whereas propagation velocity and duration were uninfluenced. The results of this study suggest that pharmacologic doses of morphine influence normal function of the LOS and possibly the distal oesophagus. The role of endogenous opiates in this respect, however, awaits further studies. It is suggested that abnormalities in opioid neurotransmission may explain some of the non-specific oesophageal motility disorders.

It has recently been shown that the oesophageal smooth muscles in addition to adrenergic and cholinergic nerves contain enkephalin immunoreactive nerves.[1] Evidence has also been presented suggesting the existence of enkephalin (opiate) receptors in the lower oesophageal sphincter of the opossum.[2 3] As endogenous opioid-like peptides (endorphins) have been identified in the central and enteral nervous system[4 5] the physiological significance of these findings remains to be clarified. Stacher *et al*[6] studied the influence of a synthetic metenkephalin analogue, FK 33-824 on oesophageal motor activity in healthy humans. Their results support a role for enkephalins in the regulation of the oesophageal wave amplitude, duration and propagation velocity. The lower oesophageal sphincter was, however, not studied. The aim of the present study was to investigate the effects of therapeutic doses of morphine on distal oesophageal motility and lower oesophageal sphincter function in man.

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Methods

SUBJECTS

Fifteen healthy volunteers, nine men and six women, aged 20–27 years (median 23 years) were investigated. None of them had a history of drug abuse or gastro-oesophageal disease. Informed written consent was obtained and the study was approved by the clinical investigation committee.

MANOMETRIC TECHNIQUE

A fluid filled recording catheter (ES 3, oesophageal manometer catheter, Arndorfer Medical Specialities, Greendale, Wisconsin, USA) consisting of three polyethylene tubes was used. Each tube had a 2 mm wide lateral opening near its distal end. The openings were placed 5 cm apart and at 120° angles (Fig. 1). The tubes were continuously perfused by a

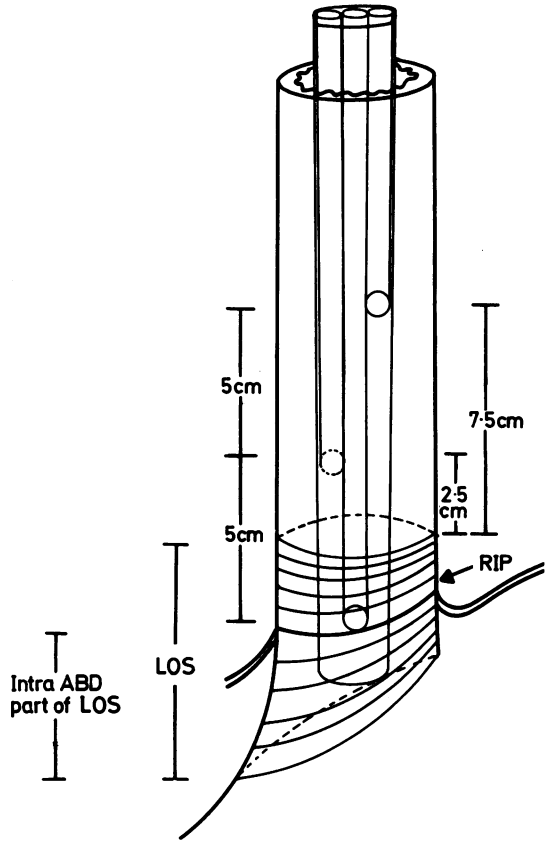

Fig. 1 *Position of recording catheter inside the distal part of oesophagus. LOS – lower oesophageal sphincter. RIP – respiratory inversion point.*

low-compliance, pneumohydraulic capillary infusion pump (Arndorfer Medical Specialities, Greendale, Wisconsin, USA) at a rate of 0·6 ml/minute. Each tube was connected to a transducer (Statham P2306, Gould, Inc, Cleveland, Ohio, USA) and in turn to a direct inkwriting recorder (Hewlett-Packard, 7774B). After topical anaesthesia of the nasal passage with 4% cocaine, the catheter was passed into the stomach of the fasting subject. The catheter was then withdrawn by 1 cm increments into the oesophagus while recordings were made. Location and length of the lower oesophageal sphincter (LOS)* was measured and the position of the respiratory inversion point (RIP) was noted. With the distal orifice just above respiratory inversion point, the catheter unit was secured by taping to the nose. The lower oesophageal sphincter pressure (LOSP) was calculated at the respiratory inversion point as the difference between basal expiratory gastric and LOS deviations. Relaxation of LOS was calculated as the deflection from the basal LOS pressure as indicated above and expressed in mm Hg and as percentage of lower oesophageal sphincter pressure (Fig. 2). Oesophageal body contractions were recorded 5·0 cm and 10·0 cm above respiratory inversion point (approximately 2·5 cm and 7·5 cm above the LOS). (Fig. 1). Amplitude of contractions (mm Hg) was measured from the oesophageal baseline to the peak of the complex. Duration of a contraction (seconds) was measured as the interval from the upstroke of the complex to its return to the baseline. Propagation velocity (cm/s) between the tube openings located 10·0 and 5·0 cm above respiratory inversion point was calculated after measuring the time interval between the peaks of corresponding complexes (Fig. 2).

* The authors are aware that the term lower oesophageal high pressure zone (LOHPZ) is more accurate and further that LOS is not equivalent to LOHPZ. From a practical point of view we, however, prefer the term LOS.

EXPERIMENTAL DESIGN

The recording catheter was passed transnasally into the oesophagus of a fasting subject and fixed as explained above throughout the study. With the subject relaxed on the examining table in the supine position, respiratory rate, pulse rate, blood pressure, pupil size and reaction to light as well as a subjective estimation of wellbeing were recorded. The volunteer was instructed to perform 10 dry swallows and 10 wet swallows (5 ml water), at 20 second intervals. The motility pattern was con-

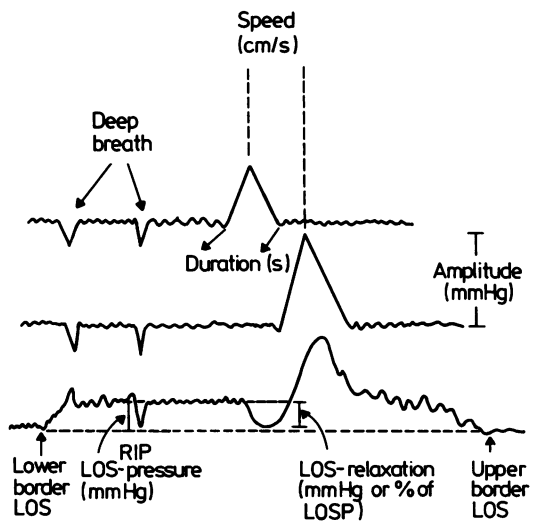

Fig. 2 *Schematic diagram of reference points used in the manometric evaluation. LOS – lower eosophageal sphincter. RIP – respiratory inversion point.*

tinuously recorded. After establishing baseline values for each subject either 0·2 mg morphine sulphate per kg body weight (10 subjects) or 1 cc saline (five subjects) was injected subcutaneously. Subjects in neither group were told whether saline or morphine was to be given at the onset of the experiment. Oesophageal and LOS recordings as well as clinical observations described above were made at 15, 30, 45, 60, and 75 minutes postinjection. Each recorded value at these intervals is the mean of five dry or wet swallows.

Table 1 *Basal oesophageal wave amplitude (mm Hg) and duration (sec) in response to dry (DS) or wet (WS) swallows. Recording positions were 5·0 and 10·0 cm above the RIP. Values are given as the mean of 10 dry and 10 wet swallows in each of 15 subjects and expressed as X±SEM.*

		5·cm (Middle orifice)	10·0 cm (Upper orifice)
Amplitude	DS	45±6	37±3
	WS	80±12	61±12
Duration	DS	4·56±0·25	4·15±0·26
	WS	5·97±0·63	4·60±0·38

ANALYSIS OF DATA

The manometric tracings were independently evaluated by two of the investigators. They had no knowledge of whether saline or morphine had been given in the tracing they were assessing. Their interpretations did not significantly differ. As normal manometric data may show a considerable variation among individuals all data were analysed *versus* basal values (=100%) using each subject as his own control. Student's *t* test was used for statistical calculations. Regression coefficient for linear correlation was calculated according to Durbin-Watson using a Minitab computer system. Data are expressed as mean±SEM.

Results

BASAL DATA OF 15 SUBJECTS

The lower oesophageal sphincter was located on an average 44·6–49·2 cm from the nostrils giving a mean sphincter length of 4·6±0·1 cm. The respiratory inversion point was located at 46·6±0·9 cm from the nostrils. Lower oesophageal sphincter pressure, expressed as the mean of three recordings, each via a separate tube, was 17·4±1·1 mm Hg. The lower oesophageal sphincter relaxation in response to dry swallows was 88±3% and in response to wet swallows 89±2%. The propagation velocities after dry and wet swallows respectively were 6·2±0·5 cm/sec and 4·3±0·4 cm/sec. Oesophageal peristaltic wave amplitude was generally higher at the distal recording point irrespective of dry or wet swallows. Likewise, the duration of the complexes was longer in the distal position (Table 1).

EFFECTS OF MORPHINE INJECTION

Lower oesophageal sphincter pressure increased slightly, although not significantly, after subcutaneous injection of morphine (Table 2). The relative relaxation of the sphincter decreased significantly with maximum effect appearing 30 minutes after the injection (Fig. 3). Linear correlation of sphincter pressure *versus* relative relaxation revealed a regression coefficient for dry swallows of −0·88 and for wet swallows of −0·83 suggesting that the decreased relative relaxation was at least partly dependent on the increased LOS-pressure. Absolute relaxation, however, also decreased as shown in Table 2. As can be seen the maximal relaxation in this respect appeared somewhat later and lasted longer than the relative relaxation. The amplitude of oesophageal waves increased slightly but insignificantly, 10·0 cm above RIP in response to wet

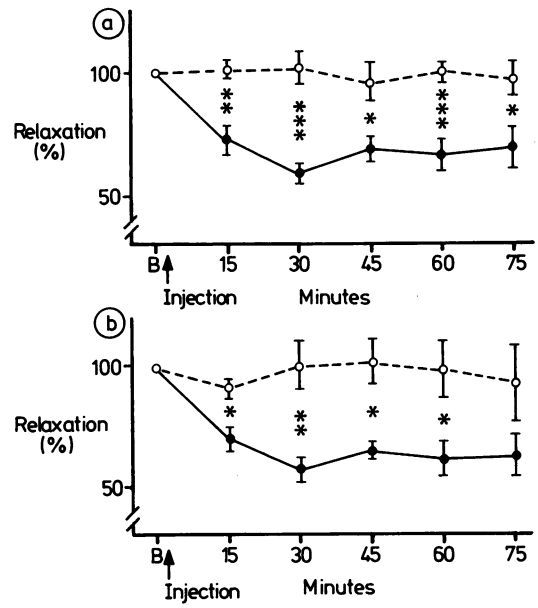

Fig. 3 *Lower oesophageal sphincter (LOS) relaxation expressed as percentage of LOS pressure in response to wet swallows (Fig. 3a) and dry swallows (Fig. 3b) before (B) and after the injection of morphine (———) or saline (– – – –). * denotes a p-value <0·05, ** denotes a p-value <0·01 and *** denotes a p-value <0·001 when tested against basal values. Mean±SEM. Saline data depicted in this figure are reproduced with kind permission from* Surg Gastroenterol.[7]

Table 2 *Lower oesophageal sphincter pressure (LOSP) and relaxation in response to dry (DS) and wet (WS) swallows before and after subcutaneous injection of morphine X±SEM. n=10.*

	Before	*15 min*	*30 min*	*45 min*	*60 min*	*75 min*
LOSP	18·8±2	20·6±2·5	23·3±3·4	22·0±2·9	22·7±1·6	23·8±1·8
DS-Relax	16·9±1·9	12·2±2·4	10·5±1·3*	11·0±1·3	10·4±1·5*	10·3±1·4*
WS-Relax	16·7±1·8	11·8±1·3*	11·1±1·1*	12·2±1·9	12·7±1·2	13·6±2·2

* Denotes p-value of <0·05 when tested *versus* basal values

swallows but were otherwise uninfluenced (Fig. 4). Oesophageal wave amplitude was not influenced after dry swallows. Duration of the peristaltic waves and propagation velocity were not influenced by morphine (Data not shown). No significant changes were observed in heart rate, respiratory rate, systolic and diastolic blood pressures. All subjects showed pupillary constriction 30–45 minutes after morphine injection. They all experienced various degrees of light headedness and euphoria within 15 minutes and felt sleepy later on.

EFFECTS OF SALINE INJECTION

The manometric parameters studied were uninfluenced by the administration of saline during 75 minutes after the injections as reported in detail elsewhere.[7] (Fig. 3) No changes were observed in the clinical parameters.

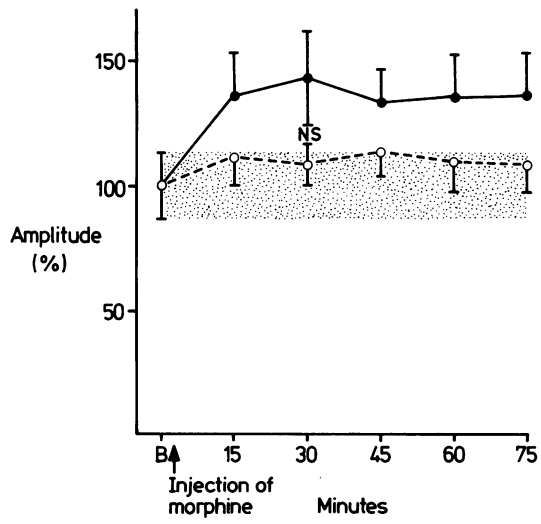

Fig. 4 *Eosophageal wave amplitude before (B) and after the injection of morphine as recorded 5·0 cm (- - - - -) and 10·0 cm (———) above the respiratory inversion point. Post injection values are expressed as percentage of basal values (B=100). Mean±SEM. Shaded area represents basal (B)±SEM amplitude.*

Discussion

Until recently it was assumed that the motility of the oesophagus and the gastroesophageal sphincter was regulated mainly by the sympathetic and parasympathetic nervous system. In addition, the role of gastrointestinal hormones, especially gastrin, and certain exogenous substances such as alcohol and coffee has been discussed in this respect. Enkephalins representing a subgroup of endorphins are found in high concentrations in neurones of the myenteric plexus of all parts of the gastrointestinal tract.[8] They are known to act as neurotransmitters and possibly as circulating hormones, too. In the oesophagus and lower oesophageal sphincter (LOS) enkephalin containing cell bodies are found abundantly. Their processes are part of the myenteric plexus which innervates the muscularis mucosa. Five distinct types of opioid receptors have been demonstrated in lower oesophageal sphincter of opossum.[3] Activation of three of these (mu, kappa and mepiridine) cause inhibition whereas stimulation of the remaining two (sigma and delta) result in contraction of LOS. Demonstration of these receptors as well as the presence of opioid containing neurones in the myenteric plexus suggest that opioids play a role in the physiological regulation of lower oesophagus and LOS. In an extensive study of a group of patients with oesophageal motility disorders Benjamin *et al*[9] tested edrophonium, bethanechol and pentagastrin as provocative drugs to reproduce the clinical symptomatology but did not consider endorphins. Stacher *et al*,[6] however, investigated the influence of a methionine enkephalin analogue, FK 33-824 on oesophageal motility of nine normal volunteers and reported an increase in amplitude and duration of peristaltic waves in the distal one-third of the oesophagus in a dose dependent fashion. They postulated that enkephalins play an excitatory role on the smooth muscle by blocking the inhibitory impulses. In earlier studies others[10 11] examined the influence of morphine and meperidine (Pethidine) on LOS function. Hall *et al*[10] in an earlier study from our laboratory showed a decrease in the pressure of LOS under the influence of morphine which increased the probability of gastro-

oesophageal reflux. Similar results were obtained by Hey *et al*[11] who found a slight dose dependent decrease of LOS-pressure after im Pethidine. The effects were abolished by iv metoclopramide.

Our study showed that parenteral injection of 0·2 mg/kg body weight of morphine into healthy young adults significantly inhibited the relaxation of LOS. The effect was maximal at 30 minutes and was still present to a lesser degree at 75 minutes after the injection (Fig. 3). In the distal one-third of the oesophagus the deglutative waves showed slight increase in magnitude but no change in duration or propagation velocity of waves between the two recording orifices situated 5·0 and 10·0 cm above the respiratory inversion. This may either be a direct influence of morphine on smooth muscle of the distal oesophagus or a compensatory response of the oesophagus to overcome a non-relaxing sphincter. The inhibitory effect on LOS relaxation was totally absent in the five subjects who were injected with saline.[7] (Fig. 3).

The divergent results of the present study when compared with others[6 10 11] may be explained by pharmacological differences of the administered substances. As indicated above there are opioid receptors of different qualities in LOS. Activation of these may thus result in stimulatory or inhibitory effects and furthermore, these effects may be dose dependent. Future studies should be done to clarify this. Another explanation is that somewhat different manometric techniques were used in the previous studies during which rapid pull through technique was used. The currently used method is superior, well established and known to give reproducible results.

Failure of LOS to relax completely under the influence of morphine in normal subjects as shown in our study is theoretically comparable to a situation which is found in achalasia. Stacher *et al*[6] observed a similar effect of FK 33-824 in their experiment, a methionine enkephalin analogue on the force of peristaltic waves in the distal part of oesophagus as we did following injection of morphine. It is therefore possible that excessive autonomous secretion of endogenous enkephalins and subsequent stimulation of specific receptors in oesophagus or LOS could result in some of the hitherto obscure non-specific oesophageal motility disorders. The use of enkephalin analogues and morphine as well as their antagonists may therefore be of value as provocative or blocking pharmacological agents during manometric examinations of such conditions. With the availability of sophisticated pneumohydraulic capillary infusion systems and application of recent information on neurotransmitters it could be possible to elucidate some of the unresolved clinical diagnoses of oesophageal pain and dysphagia.

References

1 Uddman R, Alumets J, Hakansson R, Sundler F, Walles B. Peptidergic (enkephalin) innervation of the mammalian esophagus. *Gastroenterology* 1980; **78:** 732–7.

2 McCallum RW, Dodds J, Osborne HP, Biancani P. Effect of enkephalin and other opiates on opossum lower esophageal sphincter (LES). In: Christensen J, ed. *Gastrointestinal motility*. New York: Raven Press, 1980: 37–41.

3 Rattan S, Goyal RK. Identification and localization of opioid receptors in the opossum lower esophageal sphincter. *J Pharmacol Exp Ther* 1983; **224:** 391–7.

4 Goldstein A, Tachibana S, Lowney LI, Hunkapiller M, Hood L. Dynorphin – an extraordinary potent opioid peptide. *Proc Natl Acad Sci USA* 1979; **76:** 6666–70.

5 Hughes J. Isolation of an endogenous compound from the brain with pharmacological properties similar to morphine. *Brain Res* 1975; **88:** 295–308.

6 Stacher G, Bauer P, Steinringer H, Schmierer G, Langer B, Winklehner S. Dose-related effects of the synthetic met-enkephalin analogue FK 33-824 on esophageal motor activity in healthy humans. *Gastroenterology* 1982; **83:** 1057–61.

7 Evander A, Dowlatshahi K. Distal esophageal and lower esophageal sphincter manometry in healthy volunteers. *Surg Gastroenterol* 1983; **2:** 253–9.

8 Schultzberg M, Hökfelt, T, Nilsson L *et al*. Distribution of peptide and catecholamine containing neurons in the gastro-intestinal tract of rat and guinea-pig: immunohistochemical studies with antisera to substance P, vasoactive intestinal polypeptide, enkephalins, somatostatin, gastrin/cholecystokinin, neurotensin and dopamine β-hydroxylase. *Neuroscience* 1980; **5:** 689–744.

9 Benjamin SB, Richter JE, Cordova CM, Knuff TE, Castell DO. Prospective manometric evaluation with pharmacologic provocation of patients with suspected esophageal motility dysfunction. *Gastroenterology* 1983; **84:** 893–901.

10 Hall AW, Moosa AR, Clark J, Cooley GR, Skinner DB. The effects of premedication drugs on the lower esophageal high pressure zone and reflux status of Rhesus monkeys and man. *Gut* 1975; **16:** 347–52.

11 Hey VMF, Ostick DG, Mazumder JK, Lord WD. Pethidine, metoclopramide and the gastro-esophageal sphincter. *Anaesthesia* 1981; **36:** 173–6.