Guaiacol – a new compound in the treatment of gastro-oesophageal reflux?

R V HEATLEY,* B K EVANS, J RHODES, and M ATKINSON

From the Departments of Gastroenterology and Pharmacy, University Hospital of Wales, Cardiff, and the Department of Gastroenterology, University Hospital, Nottingham

SUMMARY The effects on the oesophagus of an aromatic oil, guaiacol, has been examined in a group of 20 patients with reflux oesophagitis and also normal volunteers. This agent produced a rapid and sustained rise in resting lower oesophageal sphincter pressures and the peristaltic pressures induced in response to swallowing liquids. This compound may prove useful in the treatment of patients with reflux oesophagitis and other disorders of oesophageal motility.

Aromatic oils or substances containing them have been used as internal medicinal agents from the earliest times. The therapeutic aims have been numerous but probably the most frequent has been to produce the 'carminative' effect. Carminatives are agents which produce a sensation of abdominal warmth and relieve gastrointestinal distension when ingested orally, probably by increasing gut mucosal blood flow and acting as antispasmodics.¹⁻³ Indeed, it may have been these properties which prompted Hippocrates (460-361 BC), for example, to use oil of rue as an antispasmodic, stimulant, and rubefacient in the treatment of childhood colic.

Pharmacological studies performed on isolated preparations of mammalian smooth muscle, using known constituents of volatile oils and other chemically related agents, have demonstrated that many of these compounds decrease muscle tone and spontaneous contractility; properties which are characteristic of antispasmodics and spasmolytics.⁴ We have identified one aromatic oil, however, which increases spontaneous activity of isolated muscle strips *in vitro* and the canine colon *in vivo*.^{5,6} We have further examined the efficacy of this compound in the human oesophagus in normal individuals and patients suffering from gastro-oesophageal reflux complicated by oesophagitis. Diminution in oesophageal peristalsis and resting tone of the lower oesophageal sphincter (LOS) are believed to contribute to the pathophysiology of reflux oesophagitis and it is likely that a topically-

acting, natural product, which improves these parameters of abnormal oesophageal motility, may prove useful in the treatment of patients with gastro-oesophageal reflux.^{7,8}

Methods

PATIENTS

Twenty patients with reflux oesophagitis were studied. All patients gave a history of retrosternal burning discomfort, had demonstrable free gastro-oesophageal reflux and an associated hiatus hernia at barium meal examination, and endoscopic biopsy evidence of oesophagitis without any other demonstrable pathology. Eight normal volunteers, all of whom were asymptomatic hospital staff, were also studied by manometry.

MANOMETRY

Oesophageal manometry was performed after a six-hour fast in the left lateral position using a train of three open-ended polyvinyl chloride tubes each of 1.5 mm internal diameter with side holes 5 cm apart, perfused by a syringe pump at a rate of 0.5 ml/min and connected to Statham strain gauge pressure transducers, carrier amplifiers, and a SE3006 ultra-violet light recorder. The system showed complete fidelity to a sinusoidal input of 15 Hertz and to square pressure waves up to 60 mm Hg. Thereafter there was some attenuation, which amounted to 5% at 100 mm Hg. The rate of rise of pressure when the opening was occluded was 800 mm Hg/s.

Resting lower oesophageal sphincter pressures were measured by the rapid pull-through method taking the mean of nine measurements obtained at

* Address for correspondence: Dr R V Heatley, Department of Medicine, St James's University Hospital, Leeds LS9 7TF.

Received for publication 15 March 1982

three pull-throughs. The height of the peristaltic pressure wave in the lower oesophagus in response to swallowing 20 ml of water was also measured.^{9 10} Further recordings were taken at intervals up to 40 minutes after oral ingestion of 20 ml of the test solutions. Guaiacol, a colourless, odourless, and tasteless compound was given in varying concentrations, administered in an aqueous solution and control readings taken after a 20 ml dose of water was given alone. The test and control solutions were prepared in coded bottles by the pharmacist and given to patients in random order. Pressure measurement traces were read 'blind' by two observers working together.

GASTRIN LEVELS

Serum gastrin levels were measured by radio-immunoassay in five normal volunteers after oral administration of 20 ml 1:2500 guaiacol.¹¹

STATISTICAL ANALYSES

Results expressed are mean recordings $\pm$ SD and statistical comparisons have been performed using Student's *t* test.

Results

OESOPHAGEAL MANOMETRY

LOS pressures

The resting mean LOS pressures measured in 14 patients with reflux oesophagitis were 12.5 ± 9.1 mm Hg. Five minutes after ingestion of 20 ml of a 1:10 000 solution of guaiacol the mean LOS pressures rose to 18.9 ± 9.9 mm Hg ($p < 0.0005$) (Fig. 1). In normal individuals the baseline mean LOS pressures recorded were 17.75 ± 1.7 mm Hg and rose after 20 ml of 1:10 000 guaiacol to 32.75 ± 5.3 mm Hg ($p < 0.02$).

PERISTALTIC PRESSURES

Mean peristaltic pressure recordings taken on three recording channels after five consecutive swallows (15 readings) in 14 patients with oesophagitis are illustrated in Fig. 2. Mean baseline pressures were 24.4 ± 5.1 mm Hg and rose five minutes after ingestion of 20 ml 1:10 000 guaiacol to 30.3 ± 7.9 mm Hg ($p < 0.01$). In five patients with diffuse oesophageal spasm secondary to gastro-oesophageal reflux it was not possible to measure baseline pressures. Five minutes after guaiacol administration, the spasm had subsided sufficiently for peristaltic pressure recordings to be obtained. In normal individuals baseline peristaltic pressures were 31.75 ± 1.7 mm Hg and rose after guaiacol to 39.0 ± 6.2 mm Hg, but the difference was not significant.

Fig. 1 Mean lower oesophageal sphincter (LOS) pressures recorded in patients with reflux oesophagitis, before and five minutes after 2 mg guaiacol.

Fig. 2 Mean peristaltic pressures recorded in the lower oesophagus in response to water swallowing in patients with reflux oesophagitis, before and five minutes after 2 mg guaiacol. ▲ Pressure recordings in patients in whom peristalsis could not initially be assessed because of the presence of diffuse oesophageal spasm secondary to oesophagitis.

The manometric effects of 20 ml doses of differing concentrations of guaiacol in a further six subjects with reflux oesophagitis are illustrated in Fig. 3. Administration of 20 ml of water alone to test subjects did not significantly affect the recordings. In all cases in which a manometric effect of guaiacol was observed, this occurred within two minutes after administration and persisted 40 minutes after the dose was given.

SERUM GASTRIN LEVELS

Baseline serum gastrin levels were 43 ± 6.2 ng/ml; two minutes after guaiacol administration, 40.8 ± 1.3 ng/ml; five minutes - 43.6 ± 6.8 ng/ml; and 20 minutes after guaiacol, 40.6 ± 4.7 ng/ml. The difference was not significant.

Discussion

The term 'carminative' is probably derived from the

word, and means 'charm' and it is likely that this term aptly describes the effect these compounds have on a multitude of abdominal complaints, particularly flatulence. Indeed, peppermint oil, which contains a number of volatile oils, relaxes the lower oesophageal sphincter after oral ingestion.¹² Most essential oils exert the carminative or antispasmodic effect directly on intestinal smooth muscle probably either in the same manner as local anaesthetics or parasympathomimetic agents and may influence cellular incorporation of ATP.¹³⁻¹⁵ Some of their constituents in differing doses exert a stimulatory effect on the intestine and we have identified one compound, guaiacol, which stimulates isolated muscle strips *in vitro* and the canine colon and human oesophagus *in vivo*.

This compound almost certainly acts topically on the oesophagus and colon, the duration of onset being rapid and action prolonged. As we did not observe any significant change in serum gastrin

Fig. 3 Mean lower oesophageal sphincter (LOS) (a) and peristaltic (b) pressures recorded in patients with reflux oesophagitis, before and after varying oral doses of guaiacol.

concentrations after the administration of guaiacol it is unlikely that gastrin release is the mechanism for its actions on the oesophagus. Guaiacol has been used therapeutically for many years by mouth as an expectorant and also intravenously in patients with lung abscesses, but is not in the current *British Pharmacopoeia* (1980) or the *British Pharmaceutical Codex* (1973), apparently because of lack of use rather than any clinical problems.¹⁶ This compound appears to have potent stimulatory effects on the human oesophagus that presumably have been previously unrecognised, and may prove to be of therapeutic value in the treatment of patients with gastro-oesophageal reflux, and possibly other disorders of oesophageal motility.

Reflux of acid and bile into the oesophagus due to a reduction in tone of the lower oesophageal sphincter and delayed clearing of the oesophagus due to presumed inadequate peristalsis are features believed to be important in the development of reflux oesophagitis. Attempts to correct these abnormalities of oesophageal motility have led to the use of metoclopramide in the treatment of patients with oesophagitis. This compound has been shown to increase the lower oesophageal sphincter pressure and augment the amplitude of peristaltic contractions in the lower oesophagus in normal individuals.¹⁷ Whether it exerts these effects when given orally in normal therapeutic doses to patients with gastro-oesophageal reflux, is less clear.¹⁸ It does appear to be clinically effective in this condition, but this may be because of its known action in stimulating gastric emptying and removing acid and bile from the stomach.^{19,20} Its use, is, however, associated with side-effects in at least 10% of patients to whom it is given therapeutically.²¹ There is clearly a place for an alternative safe drug treatment which improves oesophageal motility in patients with reflux oesophagitis, and it may be advantageous in this respect to have a topically active agent. Guaiacol is a naturally occurring compound which would appear to be suitable in this regard and has been extensively used for many years with apparent safety.

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