

Effects of two anticholinergic drugs, trospium chloride and biperiden, on motility and evoked potentials of the oesophagus

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SUMMARY

Background: Anticholinergic drugs are known to impair the motor function of the oesophagus but their effects on the oesophageal afferent pathways are unknown.

Aim: To determine the effects of a peripherally-acting (trospium chloride) and a centrally-acting (biperiden) anticholinergic drug on the motility and the evoked potentials of the oesophagus.

Methods: Nine healthy volunteers were randomized to receive 1.2 mg trospium chloride (TC), 5 mg biperiden (BIP) or saline i.v. Primary peristalsis was elicited by swallowing a 5 mL water bolus and secondary peristalsis by insufflation of 20 mL air, 10 times each. Oesophageal potentials were evoked by electrical stim-

ulation in the distal and proximal oesophagus (30 stimulations at 0.4 Hz, two runs).

Results: Both anticholinergic drugs reduced by a similar amount the contraction amplitudes (TC 17 mmHg, BIP 25 mmHg, saline 67 mmHg; $P < 0.01$) and the rate of secondary contractions (TC 60%, BIP 70%, saline 95%; $P < 0.01$). In contrast, only biperiden prolonged the latencies of the evoked potentials (N1 peak, distal oesophagus: BIP 191 ms, TC 102 ms, saline 101 ms; $P < 0.01$; P1 peak: BIP 322 ms, TC 161 ms, saline 144 ms; $P < 0.01$).

Conclusions: Both anticholinergic drugs depress oesophageal motility, but only the centrally-acting anticholinergic drug biperiden modifies the oesophageal evoked potentials, suggesting a central cholinergic transmission of the oesophageal afferent pathways.

INTRODUCTION

Anticholinergic drugs are known to impair the motor function of the oesophagus by decreasing the amplitude of primary peristaltic pressure waves elicited by water swallows.^{1–6} Also, atropine has been shown to reduce the secondary oesophageal peristaltic response to balloon distension, intra-oesophageal insufflation of air, and instillation of water.⁷

The investigation of the oesophageal afferent pathways has recently been made possible by the registration of cortical evoked potentials (EPs) following electrical

stimulation⁸ or balloon distension of the oesophagus.⁹ The oesophageal EPs appear to be transmitted to the CNS by vagal afferent nerve fibres.¹⁰ The latencies of these EPs are prolonged in patients with seizures treated with anticonvulsants¹⁰ which delay non-specifically nerve conduction and synaptic transmission.¹¹ To our knowledge no data are available on the effect of anticholinergic drugs on the oesophageal EPs.

The aim of the present study was to determine the effect of the anticholinergic drugs trospium chloride (TC) and biperiden (BIP) on primary and secondary oesophageal peristalsis and on the oesophageal evoked potentials. TC, which has been shown to be a peripherally-acting anticholinergic drug,^{6, 12} cannot pass the blood-brain barrier due to its quaternary ammonium structure.¹³ In contrast, BIP rapidly passes this barrier¹⁴ and exerts central anticholinergic effects.¹⁵

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MATERIALS AND METHODS

Subjects

Nine healthy volunteers (six females, three males, aged 22–35 years) participated in the study. They had no oesophageal symptoms and were taking no medication. After explanation of the study protocol, which was in accordance with the Declaration of Helsinki and approved by the ethical committee of the Bavarian medical board, all subjects gave their written informed consent.

Study protocol

The volunteers received two catheters via the anaesthetized nose, one for electrical stimulation and the other for analysing oesophageal motility. The stimulation probe (M. Hausmann, Department of Microelectronics, Technical University of Berlin) contained a bipolar ring electrode at the tip and was connected to the stimulation device of a Nicolet Compact Four EP machine (Nicolet Instruments Ltd, Offenbach, Germany). EP stimulations were performed 5 and 15 cm above the lower oesophageal sphincter. One run included 30 stimulations with a frequency of 0.4 Hz, a duration of 200 ms and an intensity of 5 mA above the individual sensation threshold. The signal was recorded with scalp electrodes at Cz (vertex) and Fz (forehead; international EEG 10–20 system); two ground electrodes were fixed to the right forearm of the volunteers. The impedance was below 10 kOhm and the automatic artefact rejection system of the Nicolet machine was used during the measurements. The volunteers lay recumbent with open eyes fixing a point on the roof in a room without noise and with dimmed lights. The evoked potential curves were coded and stored for later analysis.

The manometric assembly (Unisensor AG, Rickenbach-Attikon, Switzerland) consisted of four strain gauge sensors at a distance of 3 cm apart and a free lumen for instillation of air between the two distal sensors. The distal sensor was positioned 3 cm above the lower oesophageal sphincter. An additional sensor was located in the pharynx to monitor swallowing. The manometric assembly was connected to a portable datalogger (Hoppe, Göttingen, Germany). After the study, the data were transferred to an IBM compatible computer, coded and stored for later analysis.

The volunteers received 1.2 mg TC, 5 mg BIP or 2 mL saline intravenously 15 min after placement of the

probes in a double-blinded manner, on different days and in a randomizd order. The measurements started 5 min after i.v. administration of the drugs or saline with two runs of electrical stimulation in the distal oesophagus. Between the two stimulation periods a resting period of 5 min was interposed to avoid habituation to the stimulus.⁸ Two runs were performed to test the reproducibility of the results. Primary peristalsis was elicited by swallowing a 5 mL water bolus and secondary peristalsis by insufflation of 20 mL of air into the distal oesophagus; each test was performed 10 times. The volunteers were not allowed to swallow between the water swallows. The distending air insufflation was given 15 s after a voluntary dry swallow, and an interval of 30 s after insufflation was observed for any response.

Finally, the stimulation probe was drawn back to a distance of 10 cm and two further runs of electrical stimulation were performed.

Data analysis

All coded data were read blindly by one of the authors (C.P.). The first negative peak N1 and the first positive peak P1 of the EP readings were identified. The latencies between the onset of stimulation and the occurrence of the peaks were measured and the N1/P1 amplitude calculated. The mean latencies and amplitude of the two runs at the distal and proximal stimulation position were compared between TC, BIP and saline in every patient. The nerve conduction velocity due to the N1 latencies of the distal and proximal stimulation points was calculated.

The mean amplitude and duration of primary peristalsis was determined 3 cm above the lower oesophageal sphincter. The incidence of failed contractions was also registered. The percentage rate of occurrence of a peristaltic contraction after air insufflation was calculated and the mean latency until onset of a secondary contraction and the amplitude of the secondary contraction were measured.

The Wilcoxon test for paired data was used to compare the effects of TC, BIP and saline on the EPs and the peristaltic response of the oesophagus.

RESULTS

The amplitude of the primary peristaltic pressure waves was significantly decreased after TC and BIP compared

Table 1. Amplitude, duration and rate of elicited primary and secondary peristalsis

	Saline	Trospium chloride	Biperiden
PP-Amp (mmHg)	67 (41–89)	17 (10–33)	25 (11–48)*
-Dur (s)	3.4 (2.9–3.8)	3.5 (2.2–4.5)	3.5 (3.0–4.1)
FP (%)	0 (0–10)	10 (0–50)	10 (0–30)†
SP (%)	95 (90–100)	60 (40–90)	70 (50–90)*
SP-Time (s)	7 (3–11)	11 (4–16)	12 (8–15)‡
SP-Amp (mmHg)	65 (40–107)	25 (11–91)	29 (14–55)*

Results are expressed as the median (range).

Primary peristalsis (PP) was elicited by swallowing 5 mL of water and secondary peristalsis (SP) by insufflation of 20 mL of air into the distal oesophagus, 10 times each.

Amp, amplitude; Dur, duration; FP, incidence of failed primary peristalsis; SP, percentage of elicited secondary contractions, SP-Time, time between insufflation and occurrence of secondary peristalsis.

*P < 0.01 biperiden vs. saline, trospium chloride vs. saline.

†P < 0.05 biperiden vs. saline, trospium chloride vs. saline

‡P < 0.01 biperiden vs. saline, P < 0.05 trospium chloride vs. saline.

to saline (Table 1). No difference was seen between TC and BIP. TC and BIP abolished peristalsis in 10% (individual range 0–50% after TC and 0–30% after BIP) of the water swallows, while only one failed peristalsis out of 120 water swallows was observed after saline ($P < 0.01$ for incidence of failed peristalsis). No difference was seen in the duration of the contractions after saline and the two anticholinergic drugs (Table 1).

The percentage of secondary contractions elicited after air distension was significantly reduced after TC and BIP with no significant difference between the two drugs (Table 1). TC and BIP also prolonged the latency until onset of the secondary contraction ($P < 0.05$) and reduced their amplitude ($P < 0.01$; Table 1).

No differences were found in the EP latencies and amplitudes at the distal and proximal stimulation level

between TC and saline, while BIP significantly prolonged the latencies of the N1 and the P1 peaks (Table 2). The N1/P1 amplitude and the nerve conduction velocity were similar after the three substances (Table 2).

DISCUSSION

Frieling *et al.*⁸ reported that cortical evoked potentials (EPs) can be recorded after electrical stimulation of the oesophagus, enabling the investigation of the sensory afferent pathways. The oesophageal EPs appear to be transmitted to the CNS by the vagal nerve.¹⁰ To our knowledge, data on the effect of anticholinergic drugs on oesophageal EPs are not available. The peripherally-acting anticholinergic drug trospium chloride (TC) did

Table 2. Latencies of the N1 and P1 peak, the N1/P1-amplitude, and the nerve conduction velocity of the oesophageal evoked potentials

	Saline	Trospium chloride	Biperiden
EP5-Lat/N1 (ms)	101 (94–128)	102 (92–136)	191 (160–262)*
-Lat/P1 (ms)	144 (130–171)	161 (138–176)	322 (228–442)*
-N1/P1-Amp (uV)	11.5 (3.3–14.1)	8.8 (4.1–25.2)	13.2 (6.5–21.7)
EP15-Lat/N1 (ms)	86 (76–114)	88 (74–100)	171 (144–245)*
Lat/P1 (ms)	131 (118–163)	133 (114–152)	307 (210–426)*
N1/P1-Amp (uV)	6.6 (3.4–18.8)	7.8 (2.7–15.4)	12.2 (6.5–16.0)
Velocity (m/s)	6.7 (4.8–9.1)	6.3 (5.0–8.3)	5.8 (4.2–7.1)

Results are expressed as the median (range).

Evoked potentials were stimulated electrically 5 cm (EP5) and 15 cm (EP15) above the lower oesophageal sphincter.

Lat, latency; Amp, amplitude.

*P < 0.01 biperiden vs. trospium chloride and vs. saline.

not influence the oesophageal EPs, while the centrally-acting anticholinergic drug biperiden (BIP) prolonged the peak latencies of these EPs. On the efferent side, both drugs strongly depressed primary and secondary peristalsis.

The observed decrease in the contraction amplitude of primary peristalsis or even an abolished peristalsis after TC and BIP is in line with the reported effects of other anticholinergic drugs such as atropine, scopolamine, hyoscyamine, cimetropium bromide and propantheline bromide.^{1–6} TC, which cannot pass the blood–brain barrier due to its quaternary ammonium structure,¹³ exerts its effect by blockade of the oesophageal muscarinic M₃ receptors of the smooth muscle,¹⁶ while the site of action is unknown for BIP. It may be located peripherally, as for TC, because BIP also blocks M₃ receptors.^{17, 18} However, the effects of BIP on primary peristalsis could also be centrally mediated by blockade of M₁ receptors in the brainstem, because focal cholinergic stimulation of the nucleus tractus solitarius and/or nucleus ambiguus in the rat have been shown to induce oesophageal peristalsis.^{19, 20}

In contrast, different results are reported on the effect of anticholinergic drugs on contraction duration. A shortened duration was found after anticholinergic drugs in two studies,^{1, 6} while, in accordance with our study, no effect was observed by others.^{3, 4} The reason might be that it is difficult to measure correctly the duration of contractions with a very low amplitude. A more accurate measurement should be possible with a strain gauge electronic pressure device such as that used in our study.

Atropine decreased the amplitude and the elicibility of secondary peristalsis induced by balloon distension, air and water insufflation.^{5, 7} In accordance with these studies, we observed a decreased rate of secondary peristalsis elicited by air insufflation after TC as well as after BIP. Thus, the effects of BIP on oesophageal primary and secondary peristalsis seem to be mediated by peripheral receptor blockade, because secondary peristalsis can be generated in the smooth muscle part of the oesophagus by the enteric nervous system independently of a central input (see Hendrix²¹). However, a central effect of BIP on secondary peristalsis cannot be excluded with certainty because vagal afferent information to the CNS has a significant effect on the regulation of oesophageal peristalsis.²¹ TC and BIP decreased not only the incidence of secondary contractions, but they also prolonged the time between air insufflation and the occurrence of the secondary

contractions and reduced their amplitudes. This points to a dual effect of anticholinergic drugs on secondary peristalsis. First, anticholinergic drugs reduce the oesophageal wall tension, resulting in a delayed stimulation of tension receptors during oesophageal distension.^{22, 23} Second, they reduce, as for primary peristalsis, the amplitude of secondary peristalsis by antagonism of the cholinergic excitation of these contractions.

After electrical stimulation of the oesophagus a regular pattern of EEG waves, the evoked potentials of the oesophagus, can be recorded by scalp electrodes.⁸ These waves were termed negative (N) and positive (P) due to the direction of the measured electrical deflections and numbered according to their order of appearance. By multichannel EEG recording techniques, positron emission tomography and magnetic resonance scan, most,^{24–27} but not all,^{28, 29} investigators located the electrical generator field of the N1 peak of the oesophageal EPs at the region of the insular cortex. The insular cortex is known to receive visceral afferents from the gut via the vagus nerve.^{30–32} The electrical generator field of the following P1 peak is assumed to be located deep in the fronto-orbital cortex or in the cingulate cortex.²⁵ The fronto-orbital cortex is involved in the sensorimotor modulation of swallowing³³ and the cingulate gyrus in the mixture of motor, sensory and visceral activities, especially for painful stimuli.²⁶

Further peaks of the oesophageal EPs, which can be seen in some patients, appear to be the result of central processing of the transferred information.²⁵

The peripherally-acting anticholinergic drug TC did not influence the oesophageal EPs. In contrast, BIP, which rapidly passes the blood–brain barrier,¹⁴ prolonged significantly the peak latencies of these EPs, suggesting a central cholinergic transmission of the oesophageal afferent pathways, because a delay in nerve conduction velocity could be ruled out as a reason for the prolongation of the latencies. There are several possible locations for these central muscarinic vagal synapses in the oesophageal afferent pathways. Reinnervation studies with transected vagal afferents,^{34, 35} and the presence of acetylcholine and choline-acetyltransferase immunoreactive fibres in vagal nodose ganglion cells^{36, 37} and in the brainstem swallowing centre in the nucleus tractus solitarius,^{38, 39} suggest that vagal afferents themselves might be cholinergic. Thalamic relay nuclei also receive some cholinergic input from the brainstem.^{40–42} The insular cortex, the

fronto-orbital cortex and the cingulate gyrus all receive dense cholinergic input.^{43, 44} However, most of these fibres derive from basal forebrain nuclei,^{45, 46} but some also derive from the thalamus.^{42, 45, 47–50}

Despite these hints of a direct cholinergic transmission of the oesophageal EPs, it cannot be ruled out that the prolongation of the latencies of the oesophageal EPs by BIP is due to an unspecific central anticholinergic effect. First, inhibition of the cholinergic input from the brainstem and from basal forebrain nuclei to GABAergic neurones in the nucleus reticularis of the thalamus results in an inhibition of thalamic relay neurones with decreased facilitation of thalamocortical signal processing.^{42, 51} Second, inhibition of cholinergic input from the basal forebrain nuclei to the cortex results in a decreased enhancement of the cortical responses to sensory information with a decreased probability of distinguishing a signal from the background cortical activity.^{51, 52}

In conclusion, while both anticholinergic drugs depress oesophageal motility, only the centrally-acting biperiden modifies the oesophageal EPs, suggesting a central cholinergic transmission of these EPs. Future studies will have to address the precise localization of the blocked muscarinic synapses in the central vagal pathways.

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