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The effect of secoverine hydrochloride on stimulated sigmoid motility: a double-blind, placebo controlled cross-over study in irritable bowel syndrome

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1 The effect of oral secoverine hydrochloride on neostigmine-stimulated sigmoid motility in 12 patients with irritable bowel syndrome was studied in a double-blind placebo-controlled cross-over study.
2 Both spontaneous and stimulated motor activity were significantly reduced by the compound in comparison with placebo. The most sensitive indices were the frequency of wave activity, maximum amplitude and motility index.
3 Two patients reported mild dizziness after secoverine.

Keywords secoverine irritable bowel sigmoid motility

Introduction

The relationship of irritable bowel syndrome (particularly abdominal pain) to disordered colonic motility has never been conclusively established although both food-stimulated hypermotility and distension of the colon have been shown to be associated with the onset of the typical symptoms (Connell *et al.*, 1965; Holdstock *et al.*, 1969; Swarbrick *et al.*, 1980).

Anticholinergic compounds have long been used in the treatment of irritable bowel syndrome. This usage is based on the theory that the symptoms are secondary to disordered motility or an abnormal response to stimulation and that by blocking muscarinic cholinergic receptors (and thus inhibiting motility) the symptoms can be relieved (Goulston, 1972).

Recently, two orally active anticholinergic compounds, clidinium bromide and cyclotropium bromide have been shown to inhibit stimulated colonic activity (Sullivan *et al.*, 1978; Stacher *et al.*, 1982).

Secoverine hydrochloride, which is a tertiary amine structurally unrelated to atropine, is an orally active muscarinic receptor blocking compound that appears from pharmacological studies in animals to be relatively selective in its activity (Zwagemakers & Claassen, 1980a,b). It has approximately 60% of the potency of atropine in blocking or inhibiting cholinergically stimulated contractions of smooth muscle, and less than 1% of the activity of atropine in inhibiting cholinergically stimulated mydriasis, salivation and lacrimation (Awagemakers & Claassen, 1981).

The aim of this study was to investigate whether oral secoverine can inhibit resting and stimulated motor activity of the sigmoid colon of patients with symptomatic irritable bowel syndrome. The stimulus chosen was intramuscular neostigmine, which has a reliable and reproducible effect on chronic motor activity (Chaudhary & Truelove, 1961b; Taylor *et al.*, 1974).

Methods

Patients

The subjects were 12 patients with symptomatic

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irritable bowel syndrome (10 females, two males; ages 18–68 years). All had been extensively screened (including a recent barium enema) to exclude an organic cause for their symptoms. The median interval since the onset of the complaint was 3.5 years.

All patients were complaining of typical abdominal pain on entry into the study (Manning *et al.*, 1978). On entry into the study and for its duration, no patients took any other medication which could influence gastrointestinal motility. The study protocol was approved by the ethics committee of Westminster Hospital and all patients gave their written informed consent.

Recording techniques

Sigmoid motor activity was studied using two constantly perfused catheters. These were made from PTFE tubing (inside diameter 2.2 mm, outside diameter 4 mm). The distal end of each was sealed and a single side hole (1.5 mm × 3.5 mm) was cut 2 cm from the tip. The catheters were fused together so that the orifices were 10 cm apart. They were each perfused with normal saline at a flow rate of 8–10 ml/h by a pressurised, constant-flow infusion system. Pressure measurements were made using Statham P23Gb strain gauge transducers. This catheter-transducer system had a resonant frequency of 12 Hz and on occluding the side-hole, a slew rate of 100 mm Hg/s. Recordings were made on a two-channel, Brush Clevite chart recorder.

Study design

The study was performed according to a prospectively randomised double-blind, placebo-controlled, cross-over design. There were two treatment sessions separated by at least 3 days at which the subjects received, in a randomised order, a single dose of 30 mg of secoverine in one session and placebo in the other.

The catheter assembly was passed into the sigmoid colon via a sigmoidoscope to a distance of 30–40 cm from the anal verge. In each case the sigmoidoscopy was passed to 25 cm and beyond the rectosigmoid junction and the catheters were observed not to be coiled in the rectum. This was confirmed in two cases by a plain X-ray. Motility recordings commenced immediately after the catheter assembly was in position. After a 30 min basal period, the test drug was taken and for the next 45 min, spontaneous activity was recorded. An intramuscular injection of 0.75 mg of neostigmine was then given and recordings continued for a further 45 min.

Study analysis

From each catheter, a basal pressure measurement was made and an arbitrary level of 2.5 mm Hg greater than basal was taken as below which any deflections were not due to changes in intraluminal pressure. Any sigmoidal pressure wave which exceeded this level was measured for maximum amplitude and duration and the frequency of such waves in the given time period was recorded. Using these data, the mean amplitude (A) was calculated and the motility index (M.I.) was derived from the formula:

$$\text{M.I.} = \bar{A} \times \frac{t}{T} \times 100$$

where t = wave duration
T = total time of measurement period

Non-parametric methods with calculation of exact probabilities were adopted for the statistical analysis of all study variables, following the principles for analysing a cross-over study design (Hills & Armitage, 1979). To estimate the direct treatment effect in the absence of any treatment with session interaction, the Hodges, Lehmann estimator was used (Lehmann, 1975).

Results

There was considerable inter- and intra-subject variation in recordings, particularly in the proximal catheter. There was a clear trend towards secoverine induced reduction or inhibition of basal and stimulated sigmoid motor activity in both catheters, but this was more obvious with the distal catheter (Table 1).

In the 45 min after administration of secoverine, the motility index was decreased in comparison with the baseline period and was significantly lower than the equivalent period in the placebo session ($P < 0.05$). A significant treatment effect ($P < 0.05$) was also observed on the frequency and maximum amplitude of wave activity and the percentage of time that the intraluminal pressure exceeded the cut-off limit of 2.5 mm Hg.

Ten of the twelve subjects showed a clear response to neostigmine, indicated by a mean seven-fold increase in the motility index during the placebo session in the period 15–30 min after injection. During the secoverine session, there was no more than a 2.5 fold increase in motility index in response to neostigmine (Figure 1). The effect of secoverine on the motility index was apparent until the end of the recording period, 45 min after the injection of neostigmine.

Table 1 Distal catheter: Estimated treatment effect, using the Hodges-Lehmann estimator, (with 95% confidence limits) of secoverine, obtained by comparing the results of session two—session one for the secoverine-placebo and placebo-secoverine treatment groups.

		Time after neostigmine (0.75 mg i.m.) (min)		
	0–45 min after study treatment	*0–15*	*15–30*	*30–45*
Frequency of wave activity (events/min)	−0.34 * (−0.56,0.0)	−0.40 ** (−1.07,0.0)	−0.32 ** (−0.89,0.0)	−0.06 NS (−1.17,0.61)
Maximum amplitude (mm Hg)	−1.5 * (−19.5,0.0)	−7.0 * (−20.5,0.0)	−6.5 ** (−26.0,−1.5)	−3.5 NS (−25.0,2.5)
Mean amplitude (mm Hg)	−1.5 NS (−2.5,0.0)	−3.5 * (−7.5,−0.5)	−2.5 ** (−18.0,0.0)	−1.0 NS (−22.5,1.0)
Mean basal pressure (mm Hg)	−1.0 NS (−6.0,2.0)	−0.5 NS (−5.0,2.0)	−1.0 NS (−4.5,2.5)	0.0 NS (−4.0,2.0)
Time pressure above 2.5 mm Hg (% of time analysed)	−5.7 * (−12.5,0.0)	−7.5 ** (−14.4,0.0)	−10.0 NS (−22.9,2.5)	−7.4 NS (−19.6,3.4)
Motility index	−23.5 * (−65.0,0.0)	−65.5 * (−183.5,−7.5)	−74.0 ** (−639.0,−5.5)	−43.0 * (−215.5,−1.5) *

*$P \leq 0.05$; ** $0.05 < P \leq 0.10$; NS = $P > 0.10$ two-sided probability from Wilcoxon two-sample rank test.

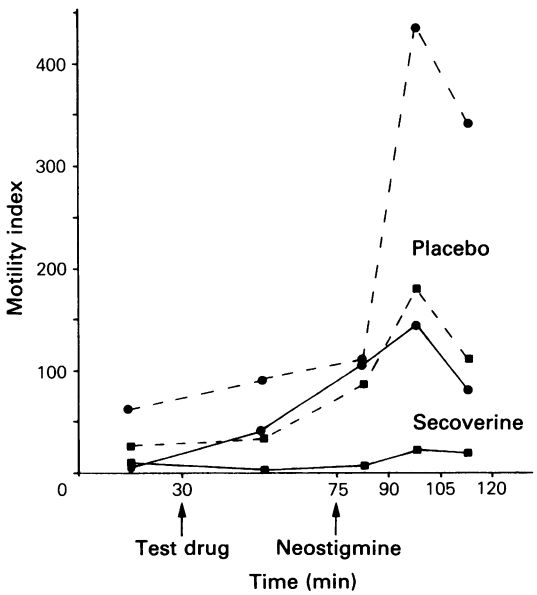

Figure 1 Mean values of motility indices. Motility was recorded continuously for 120 min; after 30 min baseline recording the study treatment was given, 45 min later 0.75 mg neostigmine was given intramuscularly. Secoverine and placebo means were calculated for each time interval for the placebo-secoverine ($n = 5$) and secoverine-placebo ($n = 7$) treatment groups separately. The values plotted are the unweighted means of the means from each treatment sequence group. ■ distal, ● proximal.

The reduction in unstimulated motility suggests that the onset of action of oral secoverine was within 45 min of ingestion. The total duration of activity of a single dose would, therefore, appear to be approximately 1 h or longer.

Two patients complained of dizziness and faintness following secoverine.

Discussion

The results of this study have indicated that orally administered secoverine in a dose of 30 mg is able to reduce motor activity in the distal colon. This dose was chosen because it had been shown in volunteers to have no serious side effects (Zwagemakers & Claassen, 1980b). However, it has recently become apparent that this may not be true of patients with irritable bowel, some of whom develop hallucinations. The systematic effect of several variables and the fact that statistical significance between secoverine and placebo could be demonstrated in a small study of only twelve patients suggest that the results are not spurious, despite the large number of variables measured and the possibility that some of the significant differences could have emerged by chance. This study was not designed to see if the drug had any effect on normal individuals or on patients with predominant diarrhoea and no pain who are often diagnosed as the painless diarrhoea form of the irritable bowel syndrome (Chaudhary & Truelove 1961a).

Chaudhary & Truelove (1961a) reported a considerable inter-subject variation in the amount of resting motor activity that occurred in the distal colon of healthy volunteers and patients with the irritable bowel syndrome (Chaudhary & Truelove, 1961b). A big inter-subject variability was also recorded in the present study although all patients included were symptomatic. One obvious reason for this variability is difference in situation of the catheters. It was not felt ethical to check the position of the catheter by X-ray of the abdomen, although this was performed in two cases as a preliminary to an oral cholecystogram. In all cases the rectosigmoid junction was negotiated and the catheters were not coiled in the rectum.

It can be argued that neostigmine, an acetylcholinesterase inhibitor, is a pharmacological rather than a physiological stimulus. However, excessive colonic sensitivity to parasympathetic stimulation has been suggested as a contributory factor in the pathophysiology of irritable bowel syndrome (Chaudhary & Truelove, 1961b). The pattern of motor activity following colonic stimulation is similar regardless of the nature of the stimulus and it may well be that a cholinergic pathway is the final common denominator (Gershon & Erde, 1981).

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