Effect of Neostigmine on Integrity of Ileorectal Anastomoses

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Summary: Patients undergoing total colectomy and ileorectal anastomosis for chronic ulcerative colitis were divided into two groups depending on whether neostigmine was administered during the anaesthetic to reverse the muscle relaxant. Those receiving neostigmine showed a postoperative anastomotic leakage rate of 36%. In the group not receiving neostigmine the leak rate was 4%, an apparently highly significant difference. Neostigmine may produce this effect by causing contractions of the gut musculature or by vasoconstriction of the blood vessels to the suture line, resulting in local ischaemia.

Introduction

Neostigmine methyl sulphate is a drug that is universally employed to reverse the action of non-depolarizing neuromuscular blocking agents used during surgery.

During the course of a total colectomy for ulcerative colitis one of us (C. B. L.) witnessed an ileorectal anastomosis being disrupted by a peristaltic wave when the abdomen was reopened to look for a swab. The neostigmine had been administered simultaneously with atropine a few minutes previously. Accordingly a retrospective study was undertaken to ascertain whether the incidence of postoperative leakage from ileorectal anastomoses in ulcerative colitis was influenced by the administration of neostigmine.

Material and Methods

The patients studied consisted of 83 cases of chronic uncomplicated ulcerative colitis. Every case operated on in the past 10 years which conformed to the criteria enumerated below was included. No acute fulminating cases of ulcerative colitis, patients with fistulae in ano, Crohn's disease, or other coincident abdominal pathology, or patients in whom the anastomosis was performed at a different time from the colectomy were included. All patients were on steroids, had normal preoperative serum electrolytes, and had an identical preoperative bowel preparation. All were operated on in the same unit by the same surgeon.

The series was divided into two groups according to the anaesthetic technique employed. In both groups anaesthesia was induced with a sleep dose of thiopentone sodium, and endotracheal intubation was facilitated by the administration of suxamethonium. Patients in group 1 were then manually ventilated with a mixture of nitrous oxide, oxygen, and cyclopropane via a circle absorption system. Small doses of tubocurarine were added but did not require reversal with anticholinesterases. Patients in group 2 were ventilated automatically with nitrous oxide and oxygen after full paralysing doses of tubocurarine had been given. Routine reversal was obtained by the simultaneous injection of atropine sulphate 1.2 mg. and neostigmine methyl sulphate 2.5 mg.

The premedication of papaveretum 20 mg. and hyoscine hydrobromide 0.4 mg. was the same in all cases, with the exception of two patients in the first group who received morphine 10 mg. and atropine sulphate 0.6 mg. and one in the second group who received pethidine 50 mg. and atropine sulphate 0.6 mg. None of these developed an anastomotic leak.

Group 1 consisted of 50 patients aged 12 to 71 years (average 30 years, standard deviation ±12.2). Group 2 comprised 31 patients aged 15 to 59 (average 31, standard deviation ±13.4).

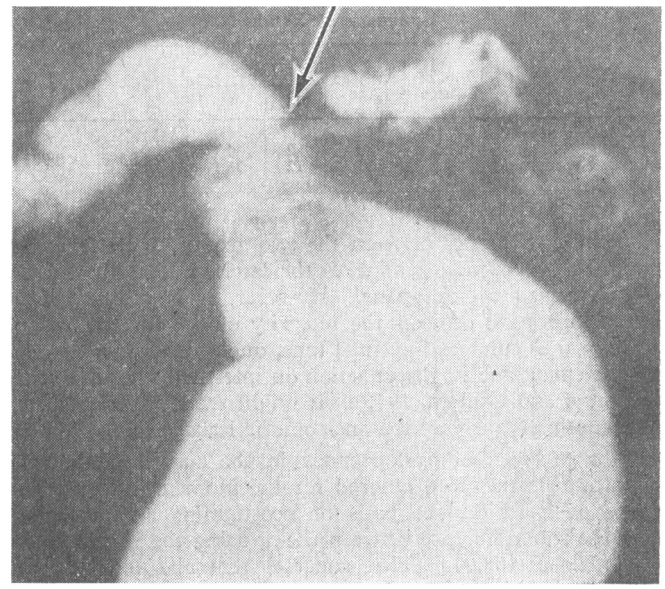

FIG. 1.—Typical leak from an ileorectal anastomosis three weeks postoperatively.

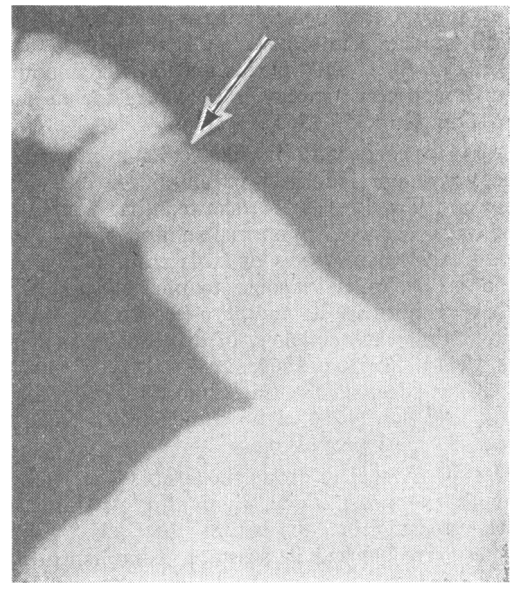

FIG. 2.—Soundly healed ileorectal anastomosis again three weeks postoperatively.

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All these patients had a protective ileostomy fashioned in continuity which was closed only if the barium enema performed routinely three weeks postoperatively failed to demonstrate a leak (Aylett, 1966). Accordingly our criterion of anastomotic leakage was in all cases radiological rather than clinical. Indeed, many patients with an obvious radiological leak would have no clinical symptoms. A typical leak is shown in Fig. 1, whereas a sound anastomosis is seen in Fig. 2.

Results

The results are summarized in the Table. Two patients out of the 50 in group 1, who did not receive neostigmine, developed a leak. On the other hand, 12 out of the 33 patients in group 2, all of whom received neostigmine, leaked from the anastomosis postoperatively. The respective percentages are 4% for the former group and 36% for the latter.

Summary of Results

	No. of Cases	Average Age	Leaks		χ^2	P
			No.	%		
Group 1. No neostigmine	50	30	2	4	14·83	<0·001
Group 2. Neostigmine	33	31	12	36		

The only difference between the two groups, apart from the administration of neostigmine to the latter, is that the former group received cyclopropane. However, it is most unlikely that cyclopropane protects the integrity of the anastomosis, as it is known to enhance intestinal tone, due to its parasympathomimetic effect, and its direct action on intestinal smooth muscle (Goodman and Gilman, 1965). It might therefore be expected to (if anything) increase the anastomotic leakage rate.

If the presence of cyclopropane in the anaesthetics of the first group be therefore ignored for the moment, and the two groups analysed on the basis of neostigmine administration being the sole difference between them, using the χ^2 test and a 2×2 table $P<0.001$. This suggests that the difference in leakage rates between the two groups is highly significant.

Discussion

It is well known that neostigmine augments motor activity in the small and large intestines. It is thought to act on the ganglion cells of Auerbach's plexus and on the smooth muscle fibres. An intact nerve supply is necessary for its full effect (Goodman and Gilman, 1965).

It appears to exaggerate normal colonic movement, and propulsive waves are increased in amplitude and frequency. Chaudhary and Truelove (1961) showed that double the total number of waves occurred in normal subjects after neostigmine, with a great increase in waves of large amplitude. Ulcerative colitics showed a similar response to normal subjects. Other workers have confirmed its motor effect on the colon while engaged in studying the aetiology of diverticulosis (Painter and Truelove, 1964 ; Painter, 1964, 1967). Other studies have shown a similar effect on the small intestine, including that of Bárány and Jacobson (1964), who demonstrated an increase in pressure activity and propulsion.

In all cases of the second group the atropine was administered together with the neostigmine, though it classically used to precede the neostigmine to ensure that all "muscarinic" receptor sites were blocked in advance. Simultaneous administration has been justified by the finding that, so far as the heart is concerned, the atropine appears to act first. Thus Kemp and Morton (1962) found that intravenous atropine took 25 seconds to produce tachycardia, whereas neostigmine needed 108 seconds to cause bradycardia. However, the same time relations need not necessarily hold good for the gut.

It is known that atropine inhibits but does not completely abolish the intestinal effects of neostigmine. Also a higher dose of atropine is needed to inhibit intestinal activity than that of sweat glands, salivary glands, the eye, or the bronchi. Atropine-resistant tone and movements of the gut have been observed (Goodman and Gilman, 1965). Doughty and Wylie (1952) found that atropine in conscious subjects appeared to have little effect in mitigating the severity of intestinal symptoms caused by neostigmine. Their results showed that administering neostigmine 1.25 mg. preceded by atropine 1.3 mg. produced unpleasant symptoms consisting of epiphora, salivation, and intestinal stimulation for 10 minutes. When neostigmine 2.5 mg. was given simultaneously with atropine 0.67 mg. to the same subject, more severe symptoms persisted for 20 minutes.

Thus although we cannot be certain when the anastomotic breakdown occurs, apart from the observation of an isolated case, it seems to us highly probable that it occurs in the early postoperative period as a result of the peroperative injection of neostigmine. The most likely explanation is that the neostigmine-induced contractions of the gut cause mechanical traction on the suture line, but an additional factor might be a diminution of the blood supply to the anastomosis during the contractions, producing irreversible ischaemia.

These effects may be brought about because the normally accepted dose of atropine is inadequate to block the "muscarinic" receptor sites in the gut, or perhaps the effects of neostigmine remain after the atropine has been destroyed by enzymatic hydrolysis. An improvement might be made by injecting the atropine first before neostigmine in the classical way, or in higher dosage. This could be tested by a prospective study.

The present study has been concerned only with the effect of neostigmine on ileorectal anastomoses in ulcerative colitics, where healthy ileum is joined to potentially diseased rectum. However, high leakage rates, varying with the age of the patient, the pathology, and the site of anastomosis, are a feature of many procedures involving gut resection, especially of the colon. Though some may be due to technical difficulty it seems possible in view of this study that many may be ascribed to neostigmine.

The overall leakage rate in the two groups is 16.8%, which is higher than the 12% quoted by Aylett (1966), whose cases we studied. This may be explained by the fact that his series includes many cases where the anastomosis was performed at a later date than the colectomy, and also all our patients were on corticosteroids, which might impair anastomotic healing.

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