

Effect of codeine and loperamide on upper intestinal transit and absorption in normal subjects and patients with postvagotomy diarrhoea

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SUMMARY Patients with chronic severe diarrhoea after truncal vagotomy and pyloroplasty are often difficult to treat using conventional antidiarrhoeal drugs and remain severely disabled. We examined the effect of two drugs, codeine phosphate and loperamide, on upper intestinal transit and carbohydrate absorption, measured non-invasively by serial exhaled breath hydrogen monitoring, in patients with postvagotomy diarrhoea who had previously failed to gain relief from drug therapy. Orocaecal transit was consistently faster in these patients than a group of controls and was associated with malabsorption of glucose. Codeine phosphate 60 mg significantly delayed transit in patients and controls and was associated with a reduction in glucose malabsorption and improvement in symptoms. Loperamide also delayed transit and improved symptoms, but the doses required for this effect (12-24 mg) were higher than usually considered necessary in secretory diarrhoea. These studies indicate that rapid intestinal nutrient transit and associated malabsorption is a factor in the development of diarrhoea postvagotomy and that symptomatic relief can be achieved in most patients by more rational use of existing drugs.

Until the introduction of effective antisecretory drugs, truncal vagotomy with pyloroplasty was a common operation in the United Kingdom for chronic duodenal ulceration. Its most significant unwanted effect, diarrhoea, was usually short lived, although for a minority of patients (2-8%) the problem has continued and remains severely disabling.¹⁻³

The exact cause for the diarrhoea in an individual patient is often difficult to ascertain. While several mechanisms have been proposed⁴⁻⁸ including bile acid malabsorption, and bacterial overgrowth,^{5,6} the major factor seems to be rapid gastric emptying and upper gastrointestinal transit which results in reduced digestion and absorption in the small intestine, and osmotic overload of the colon.⁹

Because of incomplete understanding of the aetiology, therapy remains empirical, involving dietary manipulation, bile acid binding agents^{10,11} or antibiotic therapy, in addition to regular anti-diarrhoeal drugs¹² such as codeine phosphate or loperamide. Many patients, however, do not obtain satisfactory benefit from such antidiarrhoeal therapies despite their use at doses which have measurable effects on other diarrhoeal states.^{8,13,14}

After the referral to our unit of several patients with severe postvagotomy diarrhoea, which had apparently been unresponsive to large doses of codeine and loperamide we wondered whether there might be differences in the pharmacological activity of these drugs in such patients requiring a different approach to therapy. We therefore decided to investigate the effects of codeine phosphate and loperamide on upper gastrointestinal nutrient transit and absorption in patients with postvagotomy diarrhoea, in an attempt to determine their efficacy and optimal therapeutic regimens.

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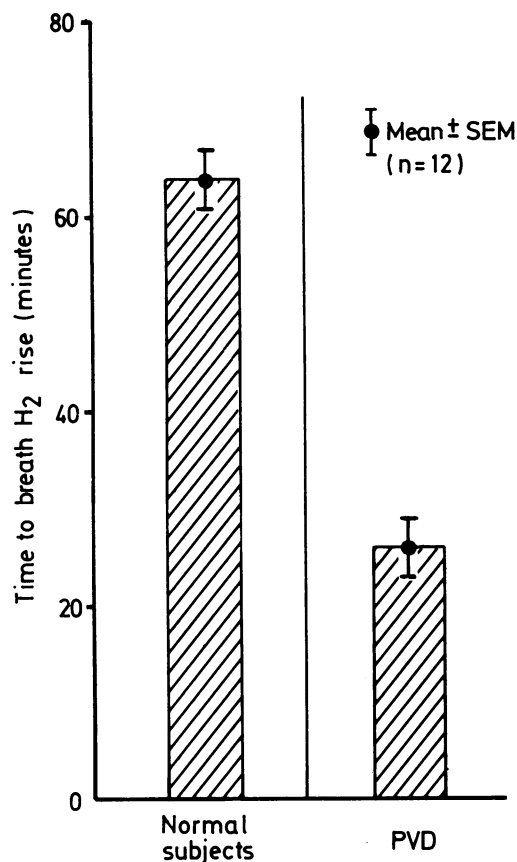


Fig. 1 Time to the breath hydrogen rise after test meal ingestion in normal subjects and patients with postvagotomy diarrhoea (PVD). PVD is associated with an earlier breath hydrogen rise compared with normal subjects, indicating accelerated oro-caecal transit.

Methods

PATIENTS AND SUBJECTS

Fourteen patients, 10 men, four women (mean age 38, range 35–67 years) with severe, chronic diarrhoea after truncal vagotomy and pyloroplasty took part in the studies, together with 12 normal volunteers (age 19–55 years), drawn from the medical personnel and student population of the hospital. All protocols were submitted to and approved by the London Hospital Ethics Committee, and patients and controls gave their informed consent before participation. Postvagotomy diarrhoea was defined as a postoperative change in bowel habit with the development of at least three or more loose motions a day, exacerbated by food. All patients had also suffered from repeated episodes of food related lower abdominal discomfort, and urgency of defeca-

tion, for at least three years. Of the 14 patients studied, 10 were regarded by their physicians as being severely incapacitated with frequency of defecation between six to eight times daily on most days.

In addition to being given standard advice on ingestion of small, dry meals and avoidance of sugary liquids, all patients had been prescribed loperamide and codeine phosphate. None, however, admitted to having derived any appreciable benefit from either drug.

Therapeutic regimens used by patients varied widely in total dosage and timing of administration. Therapies advised had ranged from 2 mg loperamide to be taken in the event of diarrhoea, to large doses of both drugs taken with or after meals. Maximum daily doses of codeine were 180 mg and loperamide 12 mg.

SELECTION OF PATIENTS FOR THE STUDIES

Patients were recruited for the two experiments in the order of their referral to the unit and their availability for repeat study. The first eight patients carried out the initial experiment, and six agreed to return for the second experiment by which time a further six patients had been recruited.

UPPER INTESTINAL TRANSIT

This was determined by the technique of serial exhaled breath hydrogen sampling.¹⁵ After an overnight fast of at least 15 hours, each individual came to the clinical study area where, after a period of 15 minutes, a series of basal exhaled breath hydrogen samples were collected using a previously described technique.¹⁶ After this basal period a standard test meal (400 ml chicken soup, HJ Heinz Ltd, 255 kcal, plus 30 ml lactulose, Duphalac, Duphar Ltd) was ingested. In a previous study¹⁷ this meal reliably produced a breath hydrogen rise in eight normal subjects who ingested the meal on three separate occasions with a mean individual coefficient of variation¹⁸ of 9%. After meal ingestion breath samples were collected at five minute intervals and then more frequently (two to three mins) once values appeared to become raised. As previously reported^{16,17} a sustained rise in breath hydrogen by more than twice the mean baseline value was taken to indicate the caecal arrival of the meal, this value being selected as in earlier studies because it offered a simple, conservative endpoint which reduced possibility of erroneous interpretation because of baseline variation. When compared in our laboratory with other previously reported end points such as time for baseline values to rise by 10 ppm,¹⁹ it provided a value which was consistently earlier by two to five minutes. The normal subjects each carried out six transit studies on separate days, receiving either no drug, codeine phosphate (30 and 60 mg) or loperamide (4,

8, 12 mg). To avoid bias, the order of experiments was randomised between individuals, and the estimation of the time to hydrogen rise from the serial data was made by one of the research team who was unaware of the drug given.

Based on the results of the normal subjects, repeated transit studies were done on eight patients using an identical method. Each patient undertook four studies in random order, receiving either no drug, loperamide (4 mg and 12 mg) or codeine phosphate (60 mg).

Because of an apparent lack of effect of loperamide on transit in the patients, seven of them consented to be restudied after ingestion of 24 mg loperamide.

GLUCOSE ABSORPTION STUDIES

Since fermentable carbohydrate that escapes absorption in the small intestine induces a rise in breath hydrogen upon its arrival at the caecum, the presence

or absence of a breath hydrogen rise after carbohydrate ingestion can be used as an index of the completeness of its absorption in the small intestine.²⁰

While others have reported that the area under the breath hydrogen curve can be used as a guide to carbohydrate malabsorption²¹ this method necessarily assumes a constant relationship between quantity of carbohydrate arriving at the caecum and size of breath hydrogen rise. Because carbohydrate fermentation products reduce caecal pH, which can autoinhibit hydrogen genesis²² this method can only be approximate. In an attempt to avoid such assumptions we recorded the presence or absence of a breath hydrogen rise after ingestion of a glucose solution (50 g in 250 ml water) which is completely absorbed in normal subjects but malabsorbed in those with post-vagotomy diarrhoea. The 12 normal subjects and 12 patients participated in this experiment.

After ingestion of the test solution serial exhaled breath hydrogen measurements were taken until at least four hours had elapsed or until a definite rise was observed (using the same criteria as the transit studies). The studies were then repeated in the patients on separate days after oral administration of either loperamide (4, 12, 24 mg), or codeine (60 mg) one hour before the glucose. The order of administration was randomised between individuals, and as in the transit studies, the interpretation of the presence and timing of a hydrogen rise was made by one individual unaware of the drug used. Carbohydrate malabsorption was said to have occurred if a breath hydrogen rise was seen which exceeded twice the mean preingestion value.

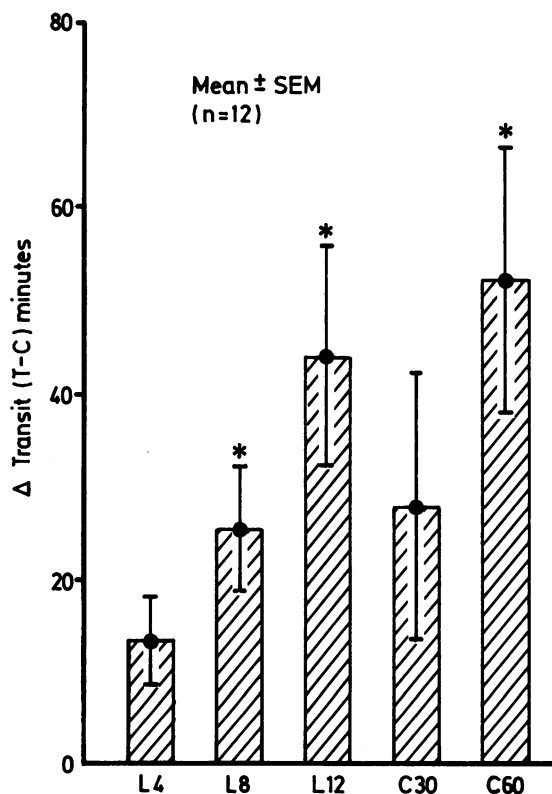


Fig. 2 This diagram depicts the changes in upper gut transit after administration of each drug in normal subjects. Values are obtained by subtracting the control values from the test data. C=codeine phosphate, L=loperamide, numbers represent the dose of the drug ingested in mg, * = p value < 0.01 .

DRUGS

All drugs used in the experiments were commercially available preparations obtained from the hospital pharmacy. Loperamide hydrochloride was given as 2 mg capsules (Immodium, Janssen Pharmaceuticals Ltd). Codeine phosphate was given as 30 mg tablets. Because data on relationships between clinical response, plasma concentrations, and the time of drug administration appear lacking for either agent in man,^{23,24} a series of pilot studies was done on one normal individual to compare the transit delay induced by 8 mg loperamide and 60 mg codeine, both drugs being taken at intervals varying between one and three hours before meal ingestion. No variation in transit delay was noted for either drug with time or drug ingestion. For purposes of experimental convenience therefore, all drugs were taken one hour before meal ingestion.

BARIUM TRANSIT STUDIES

To determine whether any breath hydrogen rise in the patients could have resulted from fermentation

by bacteria in the upper gut, rather than rapid oro-caecal transit, all patients underwent one additional transit study in which 50 ml barium (Baritop) was added to the test meal. Serial fluoroscopic inspections of the passage of barium were then made, together with breath hydrogen sampling to determine whether the onset of the rise in hydrogen concentration preceded or followed the arrival of the barium at the caecum.

CLINICAL RESPONSE TO DRUG THERAPY

All patients were asked in detail about their previous use of the two drugs. Then, to correlate the information obtained from the transit and absorption studies with the clinical response to drug therapy, 10 patients agreed whilst at home, to keep a careful diary of symptoms and to note their response to a course of drug therapy (codeine 60 mg and loperamide 4 mg or 12 mg) one of which was taken one hour before each of the three major meals of the day for at least three days.

DATA ANALYSIS

For the purposes of data display, group means and standard errors have been used. To avoid the assumption of normality of data distribution, the

Wilcoxon's matched pairs signed rank test²⁵ was used to assess the significance of differences between paired data, a value of less than 0.05 being taken to suggest that the observed differences were not due to chance.

Results

UPPER INTESTINAL TRANSIT

The results of this study are summarised in Figures 1-3.

In the normal subjects transit of the test meal was 63.3 (3.6) mins (mean (SE)). Codeine phosphate 60 mg induced a delay of 52.3 (13.1) minutes ($p < 0.01$). Codeine 30 mg also delayed transit in eight of the 12 subjects, but the overall delay for the group was less than codeine 60 mg and did not reach significance (mean delay 28.2 (14.5) mins, $p > 0.05$). Loperamide 4 mg produced only a small effect on transit (mean delay 12.3 (5.0) min $p > 0.05$) but as the dose of the drug rose, the effect increased (8 mg; mean delay 24.8 (6.8) mins, $p < 0.01$), until at 12 mg, the transit delay (43.8 (12.2) mins, $p < 0.01$), was similar to codeine 60 mg.

All the patients showed evidence of rapid oro-caecal transit with a mean time to breath hydrogen rise of 25.0 (3.5) mins ($p < 0.01$ v normal subjects, Wilcoxon's unpaired test). All patients experienced urgency of defecation and diarrhoea after the test meal, usually within 10-20 minutes of

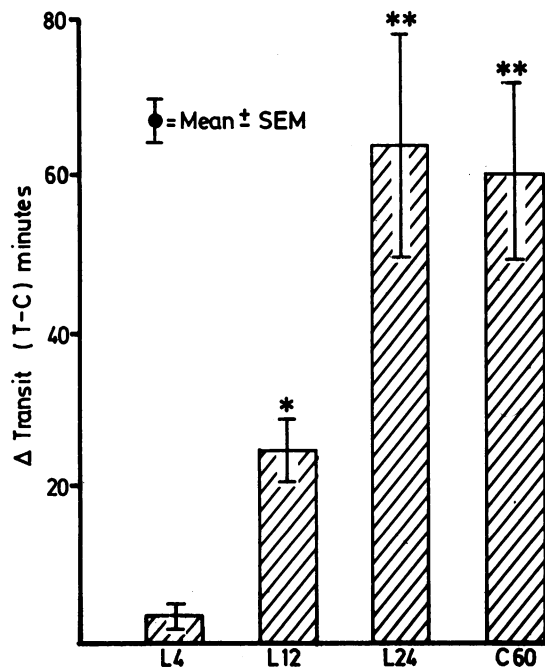


Fig. 3 Effect of codeine (60 mg) and loperamide (4, 12, 24 mg), on the time to the breath hydrogen rise in PVD patients. 24 mg loperamide is required to produce a response comparable with codeine 60 mg. * p value < 0.05 or ** < 0.01 .

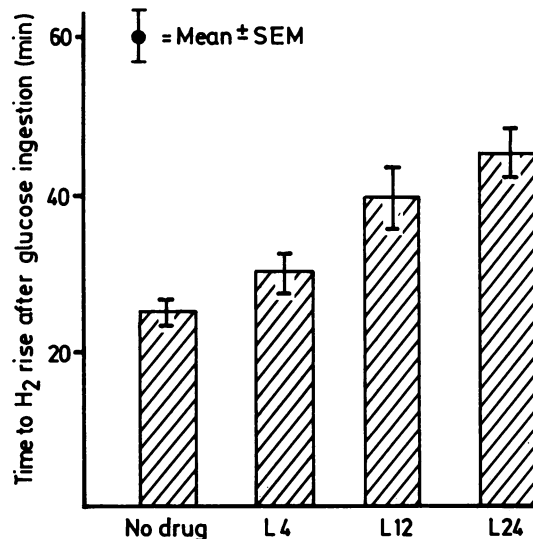


Fig. 4 Time to onset of a breath hydrogen rise after glucose ingestion in the patients, either after no drug or loperamide at 4 mg, 12 mg, or 24 mg. Although the drug failed to abolish the appearance of a breath hydrogen rise, it did progressively delay transit.

the breath hydrogen rise. In each case the rise in breath hydrogen occurred at a time when barium had already reached the caecum, indicating that the rise was unlikely to have been caused by small intestinal bacterial overgrowth. As in the normal subjects, transit was consistently delayed by codeine 60 mg (mean delay 57.8 (13.2) mins $p < 0.01$) and by loperamide 12 mg (mean delay 23.6 (9.2) mins $p < 0.05$). Loperamide 4 mg showed no significant effect (mean delay 2.0 (2.8) mins $p > 0.01$). In the seven patients given 24 mg loperamide, transit was further prolonged, mean delay 63.3 (15.8) mins $p < 0.01$.

GLUCOSE ABSORPTION

No normal subject showed a rise in breath hydrogen and none experienced abdominal discomfort or diarrhoea after ingestion of the glucose solution, indicating complete absorption in the small intestine. In contrast, all patients showed marked breath hydrogen rises after glucose, with a mean time to onset of a rise of 26.4 (2.6) minutes, indicating incomplete glucose absorption, together with reproduction of their symptoms and diarrhoea. Prior administration of codeine phosphate (60 mg) abolished the occurrence of both the hydrogen rise and symptoms, in seven of the eight patients studied. Loperamide 4 mg abolished the breath hydrogen rise and symptoms in only one patient, whereas loperamide 12 mg prevented a breath hydrogen rise and diarrhoea in two. Loperamide 24 mg given to six of those patients who had shown no response to 12 mg similarly failed to prevent a rise, although diarrhoea was prevented in three of them. Although loperamide failed to abolish the breath hydrogen rise in most patients it did, however, produce a dose dependent delay in time to onset of the rise (Fig. 4), indicating a slowing of transit.

PATIENT SYMPTOMS

All patients reported that they had been prescribed loperamide (mean dose/day 6 mg, maximal dose 12 mg daily) and codeine phosphate (mean dose/day 90 mg, maximal dose 180 mg) before the study.

Advice given on drug therapy had varied widely, ranging from small doses to be taken upon experiencing diarrhoea, to large doses taken regularly each day, in an attempt to prevent diarrhoea. None of the patients had adjusted their therapy to ensure that the drugs were taken before meals.

After being given a simple explanation of the cause of the diarrhoea, and instructed to take their drugs at least one hour before meals. Seven patients became symptom free on codeine 60 mg taken before meal ingestion. Loperamide 4 mg taken under similar circumstances improved symptoms in only three, but

increasing the dose to 12 mg produced improvement in a further three patients who had not responded to 4 mg, while in two others, a rise in dose to 24 mg controlled symptoms. Two patients failed to obtain symptomatic benefit from loperamide at any of the doses used.

Discussion

These studies confirm that severe diarrhoea in patients after truncal vagotomy is accompanied by accelerated passage of nutrient through the upper intestine and by carbohydrate malabsorption. Under these circumstances, the normal salvaging function of the colon²⁶ is likely to be overloaded and diarrhoea will occur as a consequence of an osmotic effect and stimulation of colonic secretion by malabsorbed fatty acids or bile acids.^{5 27 28}

Despite their often disappointing clinical performance, we have now found that codeine phosphate and loperamide can be used with benefit in these patients to delay upper intestinal transit to increase absorption and to relieve diarrhoea even when used in doses which had previously failed to improve symptoms.

The apparent discrepancy between lack of relief obtained from the drugs before our study and the improvement obtained during the study is rather puzzling, but is probably best explained by the timing of drug ingestion in the case of codeine and the total dose of the drug in the case of loperamide. Patients taking codeine had either not controlled the timing of the drug in relation to meal ingestion or had taken tablets with or after food. In view of the speed with which initial gastric emptying occurs after vagotomy⁴ it is likely that symptoms occurred before the drug had chance to exert an effect. While patients taking loperamide had occasionally taken doses up to 12 mg daily they had never persisted with such doses. It seems possible therefore that any clinical benefit obtained during our study was the result of persistently high dosage which may have produced a cumulative effect consequent upon the drugs prolonged biological half life (15–40 hours).²⁹

In vivo comparisons of codeine and loperamide in patients with chronic diarrhoea from a multitude of causes have indicated a rough equivalence in anti-diarrhoeal action between 4 mg loperamide and 60 mg codeine.^{13 14} In the present studies, however, we have been unable to show such a relationship. Our normal subjects required three times as much loperamide as expected, at least 12 mg was needed to induce a comparable delay in transit to 60 mg codeine, a finding similar to those of Schiller *et al*^{30 31} who in their two papers found a rough equivalence between 18 mg loperamide and 60 mg codeine in effect on transit. This relationship seems to persist in

our patients, loperamide remaining half as potent as codeine at either delaying transit or preventing the passage of glucose into the colon, or improving symptoms.

It has to be accepted that our transit method does not allow specific comment about the site of drug effect. It is well recognised, however, that the stomach is principally responsible for the rapid transit postvagotomy so it seems plausible to suggest that a reduction in gastric emptying might be the means whereby such drug effects occur. The alternative suggestion, that the transit delay was principally small intestinal, seems less likely since increased dumping, an expected sequel of small intestinal overload, was never a feature in our drug studies.

Because the excessively rapid upper intestinal transit in patients with postvagotomy diarrhoea seems to be largely the result of motor rather than secretory dysfunction, the differences in efficacy between the two drugs suggest differences in their actions on gut motility. Although both drugs are commonly regarded as being potent gastrointestinal opiate receptor agonists they show major differences in pharmacology both *in vitro* and *in vivo*. Codeine phosphate is well absorbed from the gut, produces peak plasma concentrations within minutes of ingestion,²⁴ and passes the blood-brain barrier, thus influencing both CNS and peripheral opiate receptors, either being able to delay gut transit.³⁰ Loperamide in contrast, produces little rise in plasma concentrations after ingestion, and gastrointestinal effects seem largely independent of peripheral blood levels, there being prompt removal of the drug from portal blood by the liver and re-excretion in bile.²⁹ This results in an effective enterohepatic circulation which seems to enhance loperamide's action in the gut, while reducing its extra-intestinal effects. In addition to local opiate actions, loperamide also influences intestinal secretion through a number of additional mechanisms including calmodulin inhibition,³² prostaglandin antagonism,³³ and calcium channel blockade.³⁴ Such additional actions probably explain its potent antisecretory effects both *in vitro*^{35,36} and *in vivo*³⁷ and explain why it is more effective at reducing secretory than rapid transit related diarrhoea.

Studies in animals, however, suggest that loperamide is a highly potent inhibitor of small intestinal transit (up to 40 times more potent than codeine),³⁸ but in these experiments the drug was administered parenterally and not orally. It is therefore possible that the reduced effect of loperamide we observed is related to the route of administration. Oral administration of loperamide with its marked enterohepatic recirculation reduces any effect on motility through the brainstem and paravertebral

ganglia, both of which would be influenced by codeine. An additional possibility for the reduced effect in the patients is that rapid transit of the drug might limit the time available for its reuptake in the small intestine and hence reduce the enterohepatic pool of the drug in a manner analogous to the bile salt depletion which also occurs postvagotomy.

The implications of our study therefore are that a more rational use of currently available drugs could be of benefit to patients with severe postvagotomy diarrhoea providing the chosen agent is given in sufficient quantity and at a time which enables it to influence gut motility at the onset of nutrient ingestion. Formal clinical trials based on the data we have presented now seem indicated to test this hypothesis more fully.

The final choice of drug remains a matter for debate. Codeine phosphate is cheap, appears highly effective and as in our studies, is usually not associated with central nervous side effects. In view of its potential for longer term dependency, however, it may be advisable to commence therapy with loperamide, despite its greater cost, although much larger doses than those usually recommended for diarrhoea may be necessary and therapy may be required for several days before symptomatic improvement is seen.

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