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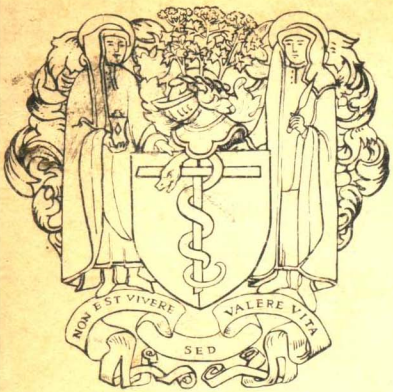

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THE CONTROL OF DIARRHOEA IN CLINICAL PRACTICE

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The Control of Diarrhoea in Clinical Practice

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D. GOUGH

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A Review of Antidiarrhoeal Compounds

J. BENNETT

It is a cliche to say that the problem of diarrhoea is universal but it has been estimated that about 4,000,000 working days a year are lost in Britain alone because of acute diarrhoea. In the main these are the presumptively infective diarrhoeas which are dealt with by the GP. There are, however, equal problems with the chronic diarrhoea which presents to the specialists who predominantly practice gastroenterology. In both these categories accurate diagnosis is difficult, and management tends to be empirical and not always particularly effective. This paper will briefly review the rather sparse knowledge about the physiological disturbances that take place in diarrhoea and then look at the available antidiarrhoeal medicines.

Physiology

There are three main physiological causes of diarrhoea. (1) *The osmotic diarrhoeas* produced predominantly by an excess of some sort of unabsorbable solute in the gut lumen, (2) *secretory diarrhoea*, in which secretion of water is greatly in excess of absorption, and (3) *motility*, resulting from an increase in the rate of gastrointestinal transit. Steatorrhoea might be considered a separate entity even though it can be ranked with other osmotically induced diarrhoeas. It is clear that in any particular disease state, more than one of these particular mechanisms may be operating.

Osmotic

This may be the result of substances administered therapeutically (e.g. $MgSO_4$ or lactulose) or occur when there is poor digestion because of malabsorption (as in coeliac disease) or following surgical resection. Thirdly, it can be due to a failure of small intestinal enzymes to break down lactose, which then acts as an unabsorbed solute lower in the GI tract.

Secretory

Infection accounts for the majority of such cases and amongst these, the most dramatic and gross example is cholera. Inflammatory bowel disease is another cause, as is the

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irritant of deconjugated bile salts on the colon. There are also the unusual endocrine syndromes (e.g. Zollinger–Ellison; Vipoma) and malabsorption of various kinds will also cause excess secretion.

Motility

Pure motility disorders are seen in endocrine disease, anxiety and the bizarre syndrome of inflammatory bowel disease that is seen so frequently but is so ill-understood.

Most muscular activity throughout the gut is segmenting activity and Fig. 1 is a

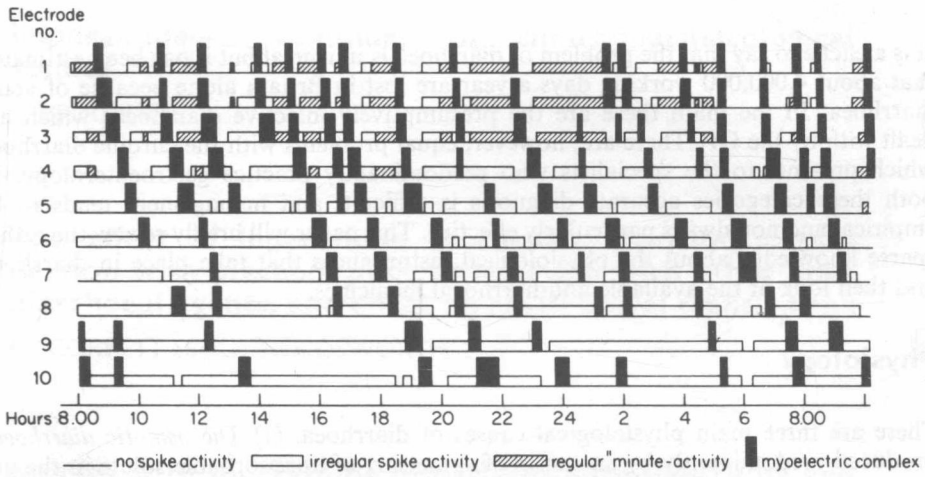

Figure 1. Schematic representation of fasting myoelectrical activity in the entire human small intestine recorded continuously during 26 h.

replication of the electrical activity although its mechanical activity closely mirrors the electrical. These are recordings made from a series of electrodes at different points down the small intestine. For about half the time there is total inactivity, i.e. where the line is flat, and there is a period of intermediate, regular spike and irregular "minute" activity phase. This is represented by the tall white columns in which a band of active peristasis, spreading over only a few centimetres of the small intestine, proceeds slowly down the length of the gut, a journey which takes about two hours. The small segment of peristasis sweeps the contents before it and this is shown diagrammatically in Fig. 2 where the active front moves along the gut behind the bolus of food thus propelling it forwards. That is about the state of our knowledge of small intestinal motility, and there is remarkably little information as to what actually happens to motility during pathological diarrhoea.

The muscular activity of the colon is again mostly segmented and variable in extent. Fig. 3 is taken from Connell's paper in which he demonstrated that, contrary to lay belief, when diarrhoea is present there is decreased activity in the gut. Usually in a normal non-diarrhoeal gut there are active contractions but when diarrhoea occurs that activity almost entirely disappears and during a phase of diarrhoea the record is almost flat. The presumptive explanation is that most of the activity one records from the gut using electrodes is segmenting activity and it is that which has been arrested. Nevertheless, by other techniques, particularly radiology, it is possible to show that

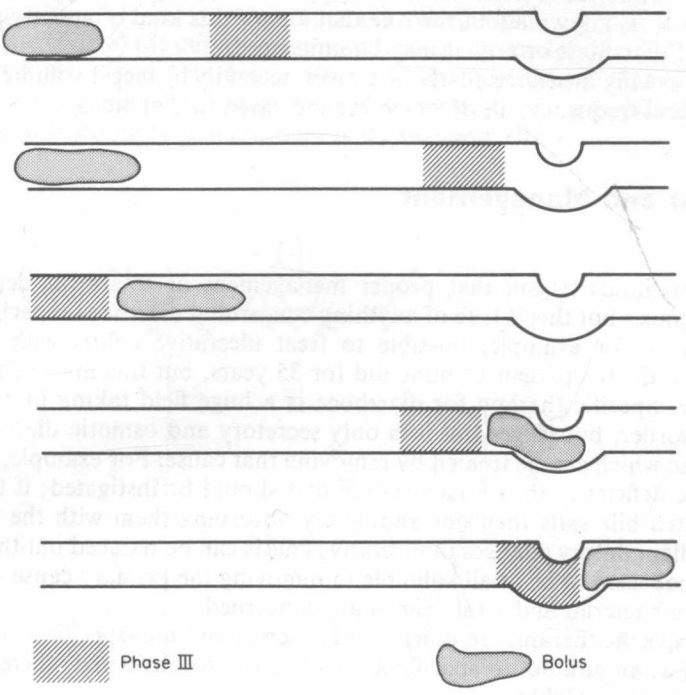

Figure 2.

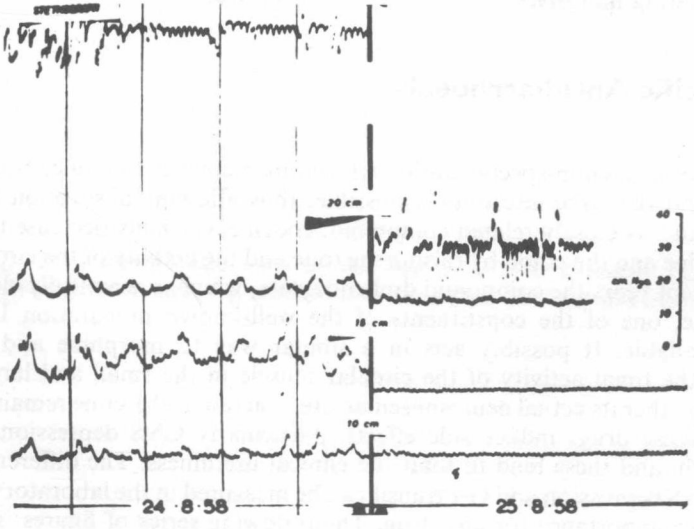

Figure 3.

propulsive waves do occur in the colon as a type of stripping activity, but once more, remarkably little is known about the role that any of this kind of activity plays in the production of diarrhoea or how it may be influenced.

Motility is usually measured firstly by transit, secondly by faecal volume output and thirdly by faecal frequency, all of which are increased in diarrhoea.

Treatment and Management

It is a platitudinous truism that proper management or treatment depends upon accurate diagnosis but this is true of anything concerning diarrhoea especially chronic diarrhoea. It is, for example, possible to treat ulcerative colitis with kaolin and morphine as a doctor/patient of mine did for 35 years, but this may be neither wise nor desirable. Specific therapy for diarrhoea is a huge field taking in almost every intestinal disorder, but in general it is only secretory and osmotic diarrhoea with a primary cause which can be treated by removing that cause. For example, if the problem is lactase deficiency then a lactose-free diet should be instigated; if the problem is deconjugated bile salts then one should try absorbing them with the appropriate resin. The inflammatory changes in ulcerative colitis can be reduced but there are very few agents that seem to be at all valuable in removing the primary cause of infection, at least where bacterial and viral origins are concerned.

Thus, the specific therapies in diarrhoea are few, and "non-specific" therapy which may be used as an adjunct to specific agents has to be considered where there is no specific treatment available.

The first group of drugs used in the non-specific treatment of diarrhoea are what might be termed the adsorbants. Kaolin and, more recently, methyl cellulose are available. They are thought to adsorb fluid, and through this, in some way to normalize the faecal frequency. It is interesting, though, that studies on ileostomy patients using these substances show that the terminal ileal output of fluid electrolytes is actually increased by these agents, so presumptively, their effects are on the colon. Apart from those few agents which are valuable in offering patients a lot of comfort, the rest seem aimed at altering motility.

Non-specific Antidiarrhoeals

The purpose of the non-specific antidiarrhoeal medicines is to reduce transit, both in the small and the large intestines if possible, thus allowing absorption to catch up. Morphine and its closely related compound, codeine, certainly decrease transit in the small intestine and the colon by raising the tone and the activity of the circular muscle. In more recent years the compound diphenoxylate, which is chemically closely related to pethidine, one of the constituents of the well-known preparation Lomotil, has become available. It possibly acts in a similar way to morphine and codeine by increasing the tonal activity of the circular muscle in the small and large intestines although whether its actual neuromuscular site of action is the same remains uncertain. However, these drugs induce side effects, particularly CNS depression, drowsiness and so forth, and these tend to limit the clinical usefulness. The difference in effects between CNS depression and G-I transit can be measured in the laboratory to establish their relative importance for any drug. The following series of figures is taken from work in the Janssen laboratories into the effects of different drugs on transit and the

analgesic effect as measured in rats by a tail withdrawal test. Morphine (Fig. 4) shows a close opposition of the two curves, while codeine (Fig. 5) is very similar. With diphenoxylate (Fig. 6) the curves are separating, i.e. the analgesic effect is less marked, requiring a higher dose than that needed to affect gut transit. Finally, loperamide (Fig. 7) shows a considerable separation between those two curves, and its effect on transit is very much more marked than is its analgesic effect.

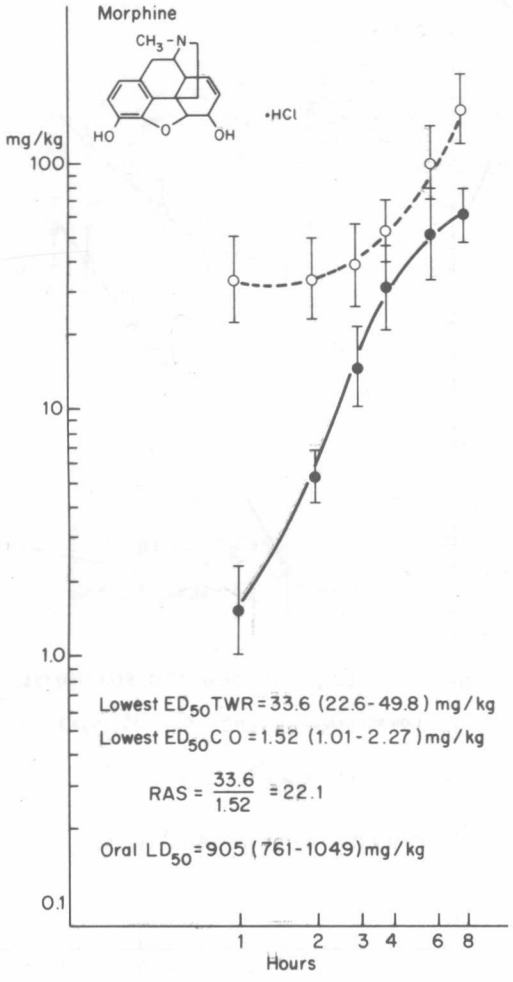

Figure 4. ED_{50} values with fiducial limits at indicated hours after castor oil (●) and in the tail-withdrawal test (○), reaction time more than 10 s with morphine.

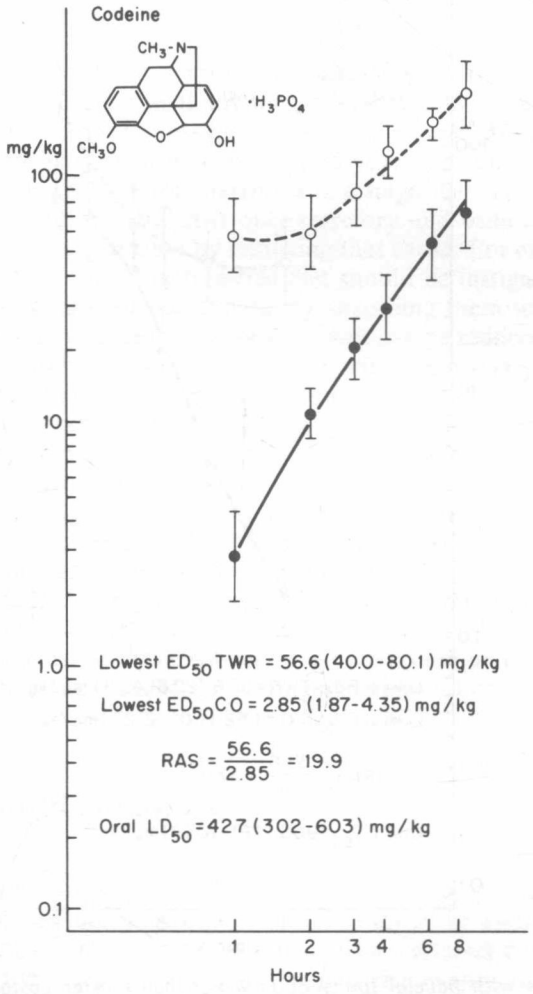

Figure 5. ED_{50} values with fiducial limits at indicated hours after castor oil (●) and in the tail-withdrawal test (○), reaction time more than 10 s with codeine.

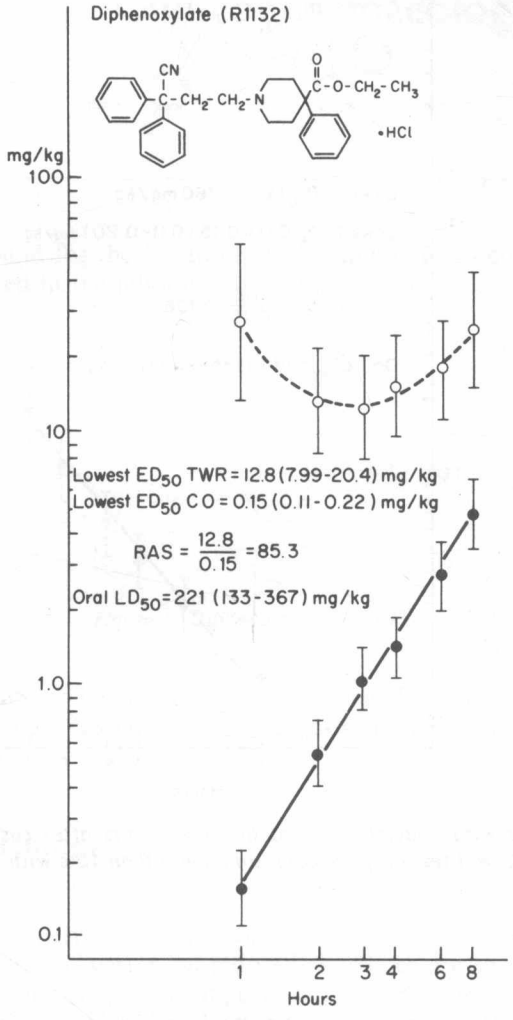

Figure 6. ED_{50} values with fiducial limits at indicated hours after castor oil (●) and in the tail-withdrawal test (○), reaction time more than 10 s with diphenoxylate.

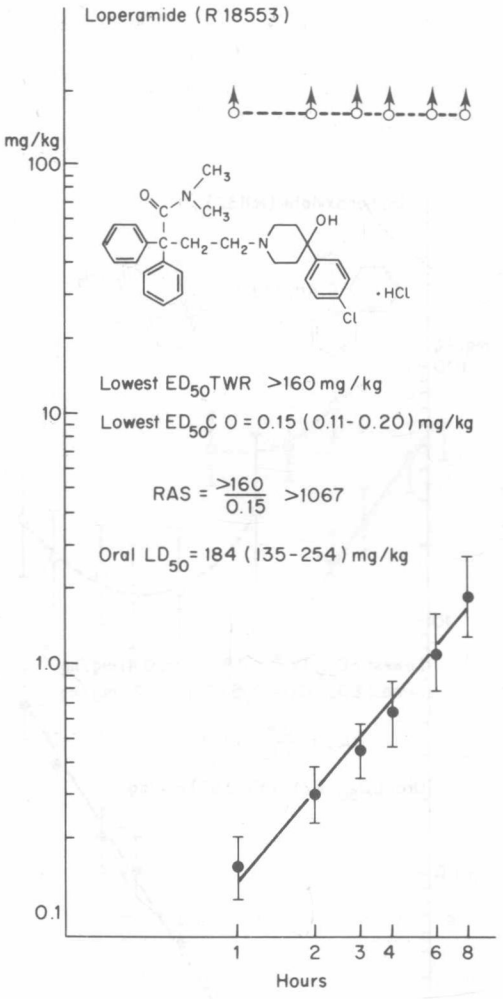

Figure 7. ED_{50} values with fiducial limits at indicated hours after castor oil (●) and in the tail-withdrawal test (○), reaction time more than 10 s with loperamide.

Conclusion

It is known that codeine diminishes the ileal output of fluid, diphenoxylate also does to a lesser extent, and loperamide may have about an equivalent action on the small intestine to that of codeine. What is required is to know how far the antidiarrhoeal effects of these drugs in man are due to changes in the small gut and how far they are to colonic alterations. Secondly, how far are these effects due to diminished forward peristasis and how much to the increase in segmenting activity? I do not think we will answer all the questions about diarrhoea in this publication nor shall we learn how to stem every tide, but at least we will make a start.

Loperamide – A Summary of Clinicopharmacological Studies

J. BRUGMANS

The starting compound for the isolation of loperamide was dephenoxylate (Fig. 1) which was synthesized in the laboratories of Janssen some ten to fifteen years ago.

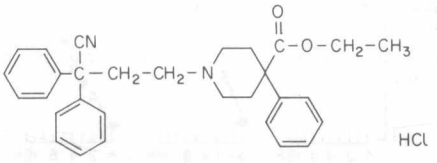

Figure 1. Diphenoxylate R 1132.

The chemical structure of loperamide is closely related to that of pethidine but the separation between the CNS effects and the gastrointestinal effects is considerably larger with loperamide.

Animal pharmacology

The antidiarrhoeal activity was measured in rats using the castor oil test which requires the prevention of castor oil-induced diarrhoea by the drug for a 1–16 h period. From the results (Fig. 3) it appears that loperamide should have a longer duration of action. This antidiarrhoeal activity is compared to the CNS effects of the drugs using the tail withdrawal test in rats, which is a measure of analgesic activity. CNS and antidiarrhoeal activity are seen at equivalent doses with codeine but there is a definite separation of activity for the other two drugs. The problem is that with loperamide, the tail withdrawal test is no longer a feasible test because the active dose in this test merges with the toxic dose which is about 100 mg/kg.

Pharmacological studies in animals having established loperamide (Fig. 2) as an

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active and selective antidiarrhoeal agent, further studies in healthy volunteers were designed to achieve three objectives:

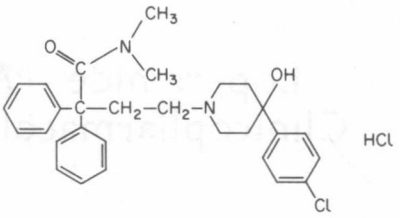

Figure 2. Loperamide R 18553.

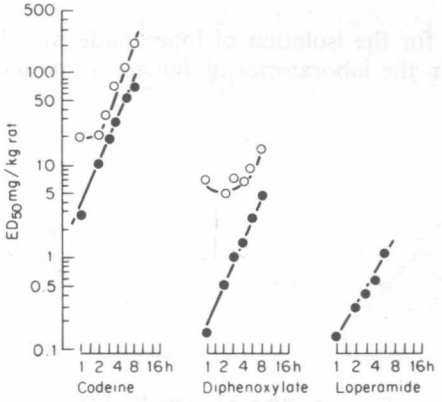

Figure 3. Comparative ED_{50} values on the tail-withdrawal test and the castor oil-induced diarrhoea test in rats.

1. to find out whether the pharmacologically predicted dose (from animal studies) is indeed active in man;
2. to compare the relative value of loperamide to that of other antidiarrhoeals;
3. to investigate whether loperamide also represents an antidiarrhoeal with a high specificity for the gastrointestinal system in man.

Study I

Loperamide, diphenoxylate and placebo were given to healthy volunteers for one week. Each day, two capsules were administered, until the subject complained of constipation or until five days had passed. As indicated in Fig. 4, two subjects discontinued medication during the placebo phase because they felt constipated, 12 subjects became constipated during the diphenoxylate period and all became constipated during the loperamide periods after about 48 h.

It can be concluded from this first study that loperamide is an active constipatory agent with a pharmacological potency that is more than twice that of diphenoxylate.

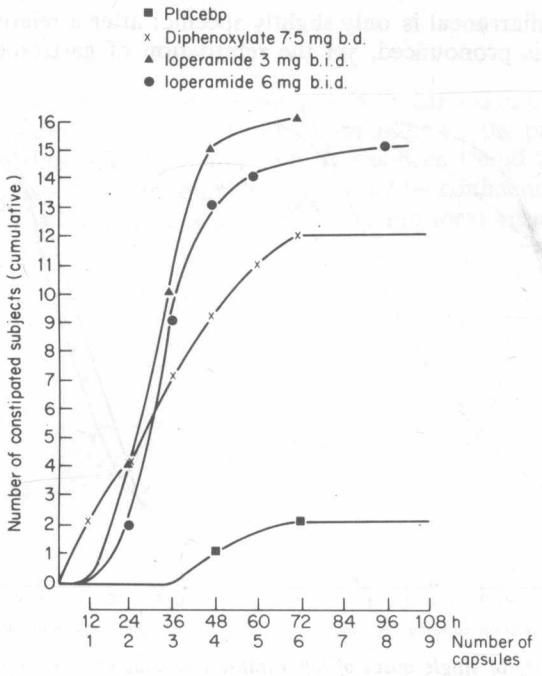

Figure 4. Comparative constipating activity of repeated dosage.

Study 2

In the second study these effective doses were compared as to their intensity and duration of action. For that purpose, the effects of single administrations were evaluated. On placebo intake, 80% of the healthy volunteers report the next defaecation within 24 h, whereas this is reported within 48 h by nearly all subjects. This normal physiological rhythm is disrupted by one single high dose (200 mg) of codeine. In most subjects, defaecation is then delayed by about 10 h; in around 20% apparent constipation is produced. With a dose of 15 or 32 mg diphenoxylate, the normal defaecation rhythm is delayed by some 17 and 27 h respectively and this pattern is still more clear-cut after loperamide. After 4, 8 and 16 mg, the next defaecation is delayed by 17, 21 and 49 h. Although these data do not permit firm conclusions to be drawn, there is reason to assume that low doses of loperamide can retard the gastrointestinal motility of patients suffering from diarrhoea.

Study 3

Pupil diameter was measured with a Polaroid camera according to the method described by Dr Jasinski from the Narcotic Research Centre in Lexington, Kentucky. On placebo intake, the pupil diameter shows a low variability; only a few times did the variability exceed 0·4 mm (Fig. 5). In contrast to placebo, pupil constriction is apparent after codeine, in nearly all cases it exceeds 0·5 mm. It may be concluded that

codeine as an antidiarrhoeal is only slightly specific: after a relatively high dose the pupil constriction is pronounced, yet the retardation of gastrointestinal motility is rather slight.

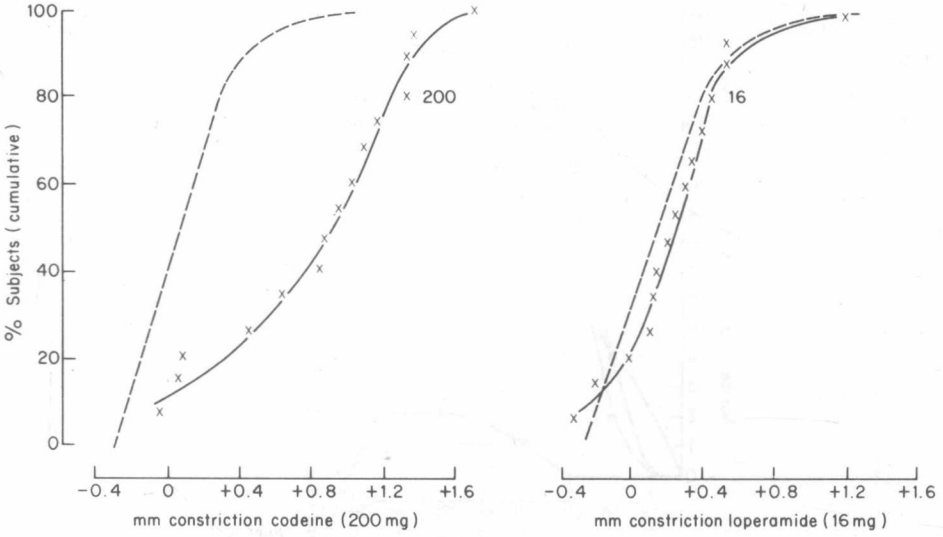

Figure 5. Activity of single doses of loperamide and codeine (- - - - placebo values).

Diphenoxylate is an antidiarrhoeal which is much more specific. It shows the reverse pattern to codeine, i.e. a marked gastrointestinal action and a slight effect on the central nervous system. Whether loperamide has a central activity is a problem which —in man at least—is hard to solve. A central activity could indeed not be demonstrated at the highest tolerated dose by the healthy volunteers. Recently, this conclusion was confirmed by Jaffe who studied 60 mg doses in subjects who used to be heroin addicts. A naloxone antagonism could be clearly demonstrated for codeine, to some extent for diphenoxylate, but not for loperamide (Fig. 6). Naloxone was given 24 h after the experimental dose and the subsequent pupil dilatation was assessed for 2 h.

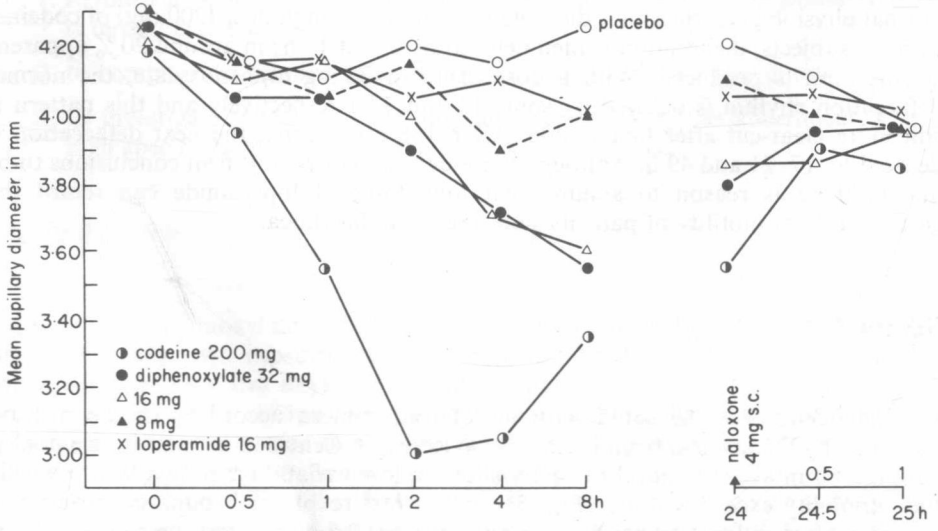

Figure 6. Pupillary activity and response to naloxone of single doses.