Effect of increasing oral doses of loperamide on gallbladder motility in man

W. P. M. HOPMAN¹, G. ROSENBUSCH², J. B. M. J. JANSEN³ & C. B. H. W. LAMERS³

¹Department of Gastroenterology and Hepatology, ²Department of Radiology, University Hospital Nijmegen, 6500 HB Nijmegen and ³Department of Gastroenterology and Hepatology, University Hospital Leiden, Leiden, The Netherlands

1 Loperamide, a peripherally acting opiate receptor agonist with antidiarrhoeal action, inhibits ileal and colonic motor function. To determine the effect of loperamide on gallbladder motility, we have pretreated five healthy volunteers with 2 mg oral loperamide 24 h, 20, 12 and 2.5 h before; six healthy volunteers with 16 mg oral loperamide 2.5 h before; and eight healthy volunteers with 16 mg oral loperamide 12 and 2.5 h before intravenous infusion of a 'physiological dose' of 12.5 pmol kg⁻¹ cholecystokinin (CCK) for 1 h to stimulate gallbladder contraction. All subjects served as their own controls. Gallbladder volume was measured by ultrasonography and plasma CCK by radioimmunoassay until 90 min after start of the CCK infusion.

2 Infusion of CCK resulted in plasma CCK concentrations similar to those after intraduodenal fat. Integrated gallbladder contraction after 4 × 2 mg loperamide (4600 ± 891% min) was similar to that without pretreatment (5270 ± 1037% min; NS). Integrated gallbladder contraction after 1 × 16 mg loperamide diminished from 5458 ± 412% min without to 2632 ± 816% min with loperamide ($P < 0.05$), and was completely abolished to -596 ± 762% min ($P < 0.0005$ vs without loperamide) after 2 × 16 mg loperamide.

3 It is concluded that loperamide inhibits gallbladder contraction in response to a physiological dose of cholecystokinin in a dose-dependent manner.

Keywords loperamide gallbladder opiate receptor agonist cholecystokinin

Introduction

Loperamide is a synthetic peripherally acting opiate agonist (Heel *et al.*, 1978), and is used primarily to treat diarrhoea. Dosages used to treat acute and chronic diarrhoea vary from 2 to 16 mg daily (Heel *et al.*, 1978). Recently, even higher dosages have been recommended (O'Brien *et al.*, 1988). Loperamide exerts its constipating effect by inhibition of ileal and colonic motor function (Heel *et al.*, 1978; Schiller *et al.*, 1984). It is not known, however, whether loperamide also affects gallbladder motility in man. Because stasis of bile is a major factor contributing to the formation of gallstones, inhibition of gallbladder emptying by loperamide could have important clinical implications (Cano *et al.*, 1986; Fridhandler *et al.*,

1983; LaMorte *et al.*, 1979; Messing *et al.*, 1983; Ryan, 1987).

The aim of the present study was therefore to determine the effect of increasing oral doses of loperamide on gallbladder contraction in man. Gallbladder contraction was induced by a physiological dose of cholecystokinin (CCK), the major hormonal mediator of postprandial gallbladder contraction (Hopman *et al.*, 1985b; Liddle *et al.*, 1985; Ryan, 1987).

Methods

The loperamide studies were carried out in three groups of healthy volunteers. All subjects were

studied in random order on two occasions, once with and once without oral loperamide (Imodium,[®] 2 mg capsules, Janssen Pharmaceutica, Goirle, The Netherlands) pretreatment. In the first group (four males, one female; aged 21–25 years) 2 mg oral loperamide was administered 24 h, 20 h, 12 h and 2.5 h before infusion of CCK, in the second group (four males, two females; aged 21–27 years) 16 mg oral loperamide was administered 2.5 h before infusion of CCK and in the third group (five males, three females, aged 22–28 years) 16 mg oral loperamide was administered 12 h and 2.5 h before infusion of CCK. After an overnight fast 12.5 pmol kg⁻¹ body weight CCK-33 (Kabi Diagnostica, Studvik, Sweden) was infused intravenously starting at 0 min over a 60 min period. Gallbladder images by real-time ultrasonography were obtained in duplicate at -20, -10 and 0 min before and subsequently every 10 min until 90 min after start of the CCK infusion. The 1 Ivy Dog Unit kg⁻¹ h⁻¹ dose of CCK was chosen, because it induced plasma CCK concentrations comparable to those found after intraduodenal fat as demonstrated in a preliminary study. In that study in six healthy volunteers (four males, two females; aged 20–27 years), on one occasion a single lumen tube was positioned in the proximal part of the duodenum under fluoroscopic control and used for perfusion of 250 ml Intralipid[®] (Kabi Vitrum, Stockholm, Sweden) during a 10 min period after an overnight fast. On the other CCK-33 was infused at a rate of 1 IDU kg⁻¹ h⁻¹ over a 60 min period.

Blood was drawn for measurement of CCK at -50, -40, -30, -20, -10 and 0 min before and at 10 min intervals until 90 min after start of the fatty meal or CCK.

Gallbladder volumes were calculated by the sum of cylinders method using a computer system (Hopman *et al.*, 1985a). The variation of volume measurements ranged from 6.0 to 22.4%. The mean of two measurements was used for further analysis. Plasma CCK concentrations were measured by a sensitive and specific radioimmunoassay using antibody T204. This antibody binds to all biologically active carboxy-terminal CCK-peptides containing the sulphated tyrosine region without cross-reactivity with gastrin-peptides (Jansen & Lamers, 1983). The detection limit of the assay was between 0.5 and 1.0 pmol l⁻¹ plasma. The intra-assay variation ranged from 4.6 to 11.5% and the inter-assay variation from 11.3 to 26.1%. Blood samples were measured in duplicate.

Results were expressed as the mean $\pm$ 1 s.e. mean. Gallbladder contraction was expressed in

percent decrease of gallbladder volume relative to basal volume (the mean of gallbladder volume at -20, -10 and 0 min). Integrated gallbladder contraction was determined by calculation of the area under the time-response curve. Statistical analysis was done by Student's *t*-test for paired and unpaired data. Informed consent was obtained from all subjects studied. The study was approved by the Ethics Committee of the Nijmegen University Hospital.

Results

Infusion of 1 IDU kg⁻¹ h⁻¹ CCK induced statistically significant increases in plasma CCK from a mean basal value of 2.0 ± 0.2 pm to a peak value of 12.2 ± 0.9 pm ($P < 0.0001$; Figure 1). Plasma CCK responses after 1 IDU kg⁻¹ h⁻¹ CCK were comparable with those obtained after intraduodenal instillation of a fatty meal (Figures 1 and 2). Infusion of CCK induced a peak plasma CCK increment of 10.7 ± 0.7 pm which was similar to that after the fatty meal, 10.2 ± 1.6 pm.

Mean basal gallbladder volumes were virtually identical in the three groups of subjects studied (16.7 ± 1.8 cm³, 17.8 ± 1.8 cm³ and 17.2 ± 1.3 cm³, NS). After pretreatment with increasing doses of loperamide basal gallbladder volumes were respectively 17.4 ± 2.2 cm³ (NS vs

Figure 1 Effect of intraduodenal administration of 250 ml 20% Intralipid on plasma CCK concentration.

Figure 2 Effect of intravenous infusion of $12.5 \text{ pmol kg}^{-1} \text{ h}^{-1}$ CCK on plasma CCK concentration.

Figure 3 Gallbladder volume in response to intravenous CCK without (●) and with (○) $4 \times 2 \text{ mg}$ loperamide pretreatment.

without loperamide), $21.3 \pm 2.9 \text{ cm}^3$ (NS vs without loperamide) and $16.0 \pm 1.8 \text{ cm}^3$ (NS vs without loperamide).

Infusion of CCK induced highly significant decreases in gallbladder volume in all three groups of subjects studied ($P < 0.05$ – $P < 0.0001$, Figures 3, 4 and 5). After pretreatment with

Figure 4 Gallbladder volume in response to intravenous CCK without (●) and with (○) $1 \times 16 \text{ mg}$ loperamide pretreatment.

Figure 5 Gallbladder volume in response to intravenous CCK without (●) and with (○) $2 \times 16 \text{ mg}$ loperamide pretreatment. Asterisks denote significant differences between the results with and without loperamide.

$4 \times 2 \text{ mg}$ loperamide, gallbladder contraction in response to CCK was similar to that without loperamide (Figure 3). Maximum gallbladder contraction, $81 \pm 6\%$, after loperamide was comparable with that without loperamide, $75 \pm 8\%$ (NS; Figure 3). Similarly, this lower dose of loperamide did not affect integrated gallbladder

Figure 6 Integrated gallbladder contraction (0–90 min) in response to intravenous CCK without (□) and with (■) increasing doses of oral loperamide. Asterisks denote significant differences between results obtained with and without loperamide pretreatment.

contraction, $4600 \pm 891\%$ min with loperamide vs $5270 \pm 1037\%$ min without loperamide (NS; Figure 6).

After 16 mg loperamide, CCK still induced a significant decrease in gallbladder volume ($P \leq 0.05$ from 40 to 80 min; Figure 4), but loperamide decreased maximum gallbladder contraction from $76 \pm 5\%$ to $45 \pm 14\%$ (NS; Figure 4), while it inhibited integrated gallbladder contraction from $5448 \pm 412\%$ min to $2632 \pm 816\%$ min ($P < 0.05$; Figure 6). After pretreatment with the higher dose of 2×16 mg loperamide, no further significant change in gallbladder volume in response to CCK was observed (Figure 5). Gallbladder volume with this higher dose of loperamide was significantly greater than that without loperamide from 10 to 90 min ($P < 0.05$ – $P < 0.0005$; Figure 5). This dose of loperamide completely abolished integrated gallbladder contraction, $-596 \pm 762\%$ min with loperamide vs $5681 \pm 342\%$ min without loperamide ($P < 0.0005$; Figure 6).

Discussion

Loperamide is widely used for the treatment of patients with diarrhoea resulting from a variety

of diseases (Heel *et al.*, 1978; O'Brien *et al.*, 1988). In contrast to other antidiarrhoeal agents like morphine and codeine, only small amounts of loperamide penetrate the central nervous system and thus its effects are generally attributed to interactions with peripheral opiate receptors. Loperamide probably exerts its antidiarrhoeal effect by a change in the motor function of the intestine, which results in increased capacitance of the gut and a delay in the passage of fluid through the intestine (Heel *et al.*, 1978; Schiller *et al.*, 1984), although some studies also suggest antisecretory activity of the drug at the intestinal level (Hughes *et al.*, 1982, 1984). The dosage of loperamide recommended for effective treatment of acute or chronic diarrhoea ranges from 2 up to 24 mg daily (Heel *et al.*, 1978; Palmer *et al.* 1980; O'Brien *et al.*, 1988).

The present study reveals that loperamide at a lower dose regimen of 8 mg daily does not affect gallbladder motility in man. However, after increasing the dose to 16 mg a reduction of gallbladder emptying to approximately 50% of control value is observed, while after increasing the dose to 32 mg gallbladder motility in response to CCK is completely abolished. The finding of an inhibitory effect of loperamide on gallbladder motility is in agreement with the observations that loperamide inhibits postprandial bilirubin output into the duodenum in patients with a short bowel syndrome (Remington *et al.*, 1982).

The results of the present study indicate that such an inhibitory action of loperamide is related mainly to an effect of loperamide on biliary tract motility, although an effect on hepatic bile secretion cannot be excluded.

It is interesting to speculate on the mechanism by which loperamide affects gallbladder motility. Since loperamide is poorly absorbed from the gastrointestinal tract and it is effectively excreted by the liver in the bile, oral ingestion of loperamide produces low plasma drug concentrations in the peripheral circulation (Heel *et al.*, 1978). There is an effective enterohepatic circulation which seems to enhance loperamide's action in the gastrointestinal and biliary tract (Heel *et al.*, 1978; Killinger *et al.*, 1979). At these sites, loperamide interacts with opiate receptors which have been located among other places, in the duodenal mucosa, cystic duct and gallbladder (Ambinder & Schuster, 1979; Giagnoni *et al.*, 1983; Heel *et al.*, 1978; Makhlof, 1987; Miyazaki *et al.*, 1982). In contrast to morphine which reduces gallbladder contraction in response to both a fatty meal and CCK, loperamide lacks central opiate effects (Heel *et al.*, 1978; Sacchetti *et al.*, 1976; Worobetz *et al.*, 1982). The present observations, therefore, suggest

that peripheral opiate receptors are involved in the inhibitory action of loperamide on CCK induced gallbladder contraction. Opiates increase duodenal muscle tone and inhibit propulsive activity (Ambinder & Schuster, 1982; Heel *et al.*, 1978; Rowlands *et al.*, 1950). Theoretically, it is possible that obstruction of the sphincter of Oddi or cystic duct accounts for inhibition of gallbladder emptying. However, because loperamide was without effect on basal gallbladder volume, interference of loperamide with gallbladder contraction at the level of the gallbladder either by a direct effect on smooth muscle or via an intermediate step such as a nervous pathway, seems more likely.

CCK is of major importance in mediating gallbladder contraction to meals of different composition (Hopman *et al.*, 1985b; Liddle *et al.*, 1985; Ryan, 1987). The mechanism of action of CCK on gallbladder smooth muscle is only poorly understood (Ryan, 1987). Gallbladder contraction in response to CCK was inhibited by somatostatin, pancreatic polypeptide and atropine (Fisher *et al.*, 1985, 1987; Greenberg *et al.*, 1978; Gullo *et al.*, 1984). The finding of an inhibitory effect of loperamide on CCK induced

gallbladder contraction indicates that beside these regulatory peptides and the cholinergic system, CCK induced gallbladder contraction is also affected by locally acting opiates and possibly opioid peptides.

The results of the present study may have clinical implications. Regular gallbladder emptying is needed to prevent sludge and gallstone formation (Cano *et al.*, 1986; Fridhandler *et al.*, 1983; Lamorte *et al.*, 1979; Messing *et al.*, 1983; Ryan, 1987). Therefore patients on loperamide treatment are at an increased risk of bile stasis and subsequent development of cholelithiasis. Clinicians prescribing loperamide, particularly at higher doses, should be aware of this possible adverse effect.

In conclusion, loperamide inhibits cholecystokinin induced gallbladder contraction in a dose dependent manner. This finding is compatible with the hypothesis that cholecystokinin induces gallbladder contraction by an opiate-sensitive mechanism.

The authors are indebted for technical assistance to H. J. A. Mulders.

References

- Ambinder, R. F. & Schuster, M. M. (1979). Endorphins: New gut peptides with a familiar face. *Gastroenterology*, **77**, 1132–1140.
- Cano, N., Cicero, F., Ranieri, F., Martin, J. & Di Constanzo, J. (1986). Ultrasonographic study of gallbladder motility during total parenteral nutrition. *Gastroenterology*, **91**, 313–317.
- Fisher, R. S., Rock, E., Levin, G. & Malmud, L. S. (1987). Effects of somatostatin on gallbladder emptying. *Gastroenterology*, **89**, 885–890.
- Fisher, R. S., Rock, E. & Malmud, L. S. (1985). Cholinergic effects on gallbladder emptying in humans. *Gastroenterology*, **89**, 716–722.
- Fridhandler, T. M., Davison, J. S. & Shaffer, E. A. (1983). Defective gallbladder contractility in the ground squirrel and prairie dog during the early stages of cholesterol gallstone formation. *Gastroenterology*, **85**, 830–836.
- Giagnoni, G., Casiraghi, L., Senini, R., Revel, L., Parolaro, D., Sala, M. & Gori, E. (1983). Loperamide: evidence of interaction with μ and δ opioid receptors. *Life Sci.*, **33** suppl. 1, 315–318.
- Greenberg, G. R., Adrian, T. E., Baron, J. H., McCloy, R. F., Chadwick, V. S. & Bloom, S. R. (1978). Inhibition of pancreas and gallbladder by pancreatic polypeptide. *Lancet*, **ii**, 1280–1282.
- Gullo, L., Bolondi, L., Priori, P., Casanova, P. & Labò, G. (1984). Inhibitory effect of atropine on cholecystokinin-induced gallbladder contraction in man. *Digestion*, **29**, 209–213.
- Heel, R. C., Brogden, R. N., Speight, T. M. & Avery, G. S. (1978). Loperamide: a review of its pharmacological properties and therapeutic efficacy in diarrhoea. *Drugs*, **15**, 33–52.
- Hopman, W. P. M., Brouwer, W. F. M., Rosenbusch, G., Jansen, J. B. M. J. & Lamers, C. B. H. W. (1985a). A computerized method for rapid quantification of gallbladder volume from real-time sonograms. *Radiology*, **154**, 236–237.
- Hopman, W. P. M., Kerstens, P. J. S. M., Jansen, J. B. M. J., Rosenbusch, G. & Lamers, C. B. H. W. (1985b). Effect of graded physiologic doses of cholecystokinin on gallbladder contraction measured by ultrasonography. *Gastroenterology*, **89**, 1242–1247.
- Hughes, S., Higgs, N. B. & Turnberg, L. A. (1982). Antidiarrhoeal activity of loperamide; studies of its influence on ion transport across rabbit ileal mucosa *in vitro*. *Gut*, **23**, 974–979.
- Hughes, S., Higgs, N. B. & Turnberg, L. A. (1984). Loperamide has antisecretory activity in the human jejunum *in vivo*. *Gut*, **25**, 931–935.
- Jansen, J. B. M. J. & Lamers, C. B. H. W. (1983). Radioimmunoassay of cholecystokinin in human tissue and plasma. *Clin. Chim. Acta*, **131**, 305–316.
- Killinger, J. M., Weintraub, H. S. & Fuller, B. L. (1979). Human pharmacokinetics and comparative bioavailability of loperamide hydrochloride. *J. clin. Pharmacol.*, **19**, 211–218.
- La Morte, W. W., Schoetz, D. J. Jr., Birkett, D. H. &

- Williams, L. F. Jr. (1979). The role of the gallbladder in the pathogenesis of cholesterol gallstones. *Gastroenterology*, **77**, 580–592.
- Liddle, R. A., Goldfine, I. D., Rosen, M. S., Taplitz, R. A. & Williams, J. A. (1985). Cholecystokinin bioactivity in human plasma. Molecular forms, responses to feeding, and relationship to gallbladder contraction. *J. clin. Invest.*, **75**, 1144–1152.
- Makhlouf G. M. (1987). *Isolated smooth muscle cells of the gut*, ed. Johnson, L. R., vol. 1, 2nd edition, pp 555–569. New York: Raven Press.
- Messing, B., Bories, C., Kunstlinger, F. & Bernier, J. (1983). Does total parenteral nutrition induce gallbladder sludge formation and lithiasis? *Gastroenterology*, **84**, 1012–1019.
- Miyazaki, H., Nambu, K. & Hashimoto, M. (1982). Loperamide in rat intestines: a unique disposition. *Life Sci.*, **30**, 2203–2206.
- O'Brien, J. D., Thompson, D. G., McIntyre, A., Burnham, W. R. & Walker, E. (1988). Effect of codeine and loperamide on upper intestinal transit and absorption in normal subjects and patients with postvagotomy diarrhoea. *Gut*, **29**, 312–318.
- Palmer, K. R., Corbett, C. L. & Holdsworth, C. D. (1980). Double blind cross-over study comparing loperamide, codeine and diphenoxylate in the treatment of chronic diarrhoea. *Gastroenterology*, **79**, 1272–1275.
- Remington, M., Fleming, C. R. & Malagelada, J. R. (1982). Inhibition of postprandial pancreatic and biliary secretion by loperamide in patients with short bowel. *Gut*, **23**, 98–101.
- Rowlands, E. N., Chapman, W. P., Taylor, A. & Jones, C. M. (1950). Multiple balloon kymograph recording of the comparative action of morphine and placebos on the motility of the upper small intestine in man. *Surg. Gynecol. Obstet.*, **91**, 129–137.
- Ryan, J. P. (1987). Motility of the gallbladder and biliary tree. In *Physiology of the gastrointestinal tract*, ed. Johnson, L. R., vol. 1, 2nd edition, pp 695–721. New York: Raven Press.
- Sacchetti, G., Roncoroni, L., Mandelli, V., Rocca, F. & Magni, E. (1976). Effect of analgesic agents on emptying of the gallbladder in man. *Eur. J. clin. Pharmac.*, **10**, 127–131.
- Schiller, L. R., Santa Ana, C. A., Morawski, S. G. & Fordtran, J. S. (1984). Mechanism of the anti-diarrheal effect of loperamide. *Gastroenterology*, **86**, 1475–1480.
- Worobetz, L. J., Baker, R. J., McCallum, J. A., Wells, G. & Sullivan, S. N. (1982). The effect of naloxone, morphine and an enkephalin analogue on cholecystokinin octapeptide-stimulated gallbladder emptying. *Am. J. Gastroenterol.*, **77**, 509–511.

(Received 10 April 1989,
accepted 7 September 1989)