Misoprostol induces gallbladder contraction during fasting, but does not influence postprandial emptying : an ultrasound study in healthy subjects

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Abstract

Objective : **The aim of this study was to evaluate the effect of the PGE_1 analogue, Misoprostol, on gallbladder fasting volume and meal-stimulated emptying. Prostaglandins' effects on the gallbladder were studied principally regarding mucus production during lithogenesis. In the few *in vitro* and *in vivo* studies, contradictory results concerning their influence upon gallbladder motility were obtained.**

Subjects : **13 healthy subjects, 8 females, 5 males, aged 23.4 years (ranges 22-25).**

Methods : **Gallbladder volumes were assessed by ultrasound, after measuring the three diameters of the gallbladder in two perpendicular planes, using a conventional 2D equipment and a 3D equipment, after the 3D-reconstruction of the gallbladder. The volumes were calculated by means of the ellipsoid formula. Gallbladder emptying variables (residual volume, ejection fraction, area under emptying curve) were assessed during 90 minutes after a test meal (14 g fat, 425 kcal). Gallbladder emptying was evaluated in each subject on three different days : without prior Misoprostol administration, after 200 mg Misoprostol, and after 400 mg Misoprostol. Misoprostol was given orally as a single dose, 60 minutes before the meal. The two-tailed Student's t test for paired observations was used to compare the results.**

Results : **Misoprostol induced a significant decrease of the gallbladder fasting volume : from 12.8 ± 4.4 (SD) ml (controls) to 9.1 ± 3.6 ml (200 mg Misoprostol) and 5.4 ± 2.6 ml (400 mg Misoprostol). Gallbladder meal-stimulated emptying was not influenced by Misoprostol.**

Conclusions : **Our results indicated that, in healthy subjects, misoprostol induced a dose-dependent gallbladder emptying in the fasting state, but did not influence gallbladder postprandial emptying. Pre-prandial Misoprostol administration might be useful to treat gallbladder stasis in patients with chronic constipation, thus preventing gallstone formation.** (Acta gastroenterol. belg., **2002**, 65, **191-195**).

Key words : prostaglandins, misoprostol, gallbladder emptying, ultrasound.

Introduction

Since the early 1970s there has been an increasing interest shown in the role of prostaglandins in the gastrointestinal tract. Prostaglandins, especially in the E series, play an important role in gastrointestinal physiology and pathophysiology. Prostaglandins have been found to influence gastric acid production and cytoprotection (1), gastric emptying (2), intestinal motility and intestinal fluid movement (3). Prostaglandins' effects on the gallbladder were mainly studied regarding mucus production during gallstone formation. In the few studies performed *in vitro* or *in vivo* on gallbladder motility (4-6), contradictory results were obtained, mainly due to the different species studied and to the type and concentration of prostaglandins used.

We undertook the present study in order to evaluate the effect of Misoprostol, the synthetic PGE_1 analogue, on gallbladder fasting volume and on gallbladder meal-stimulated emptying in healthy subjects.

Materials and Methods

Subjects

We studied 13 healthy volunteers, 8 females and 5 males, aged 23.4 (ranges 22-26). Their mean BMI was 20.4 ± 2 kg/m^2. All subjects had normal gallbladder at ultrasonography. Informed consent was obtained from each subject before examination. The study protocol was approved by the Ethical Committee of the University.

Method

The ultrasound evaluation was carried out after an overnight fast (12 hours). None of the subjects took any medication that might have influenced gallbladder motility for 24 hours and none smoked on the morning of the study. None of the volunteers was taking oral contraceptive pills.

The gallbladder fasting and postprandial volumes were calculated by ultrasound after measuring three diameters (length, width and depth) in two perpendicular planes by conventional 2D examination (Fig. 1) and also after the 3D reconstruction of the gallbladder (Fig. 2). Measurements were performed using a Voluson 530D, Kretz equipment and a dedicated 3D multi-frequency probe. The ellipsoid formula was used to calculate gallbladder volumes (7).

After assessment of the fasting gallbladder volume (FV), subjects were requested to eat a solid-liquid meal consisting of one slice of bread (30 g), butter (10 g), one boiled egg, and tea (300 ml) with sucrose (25 g). The test meal was equivalent to 14 g fat and 425 kcal (8).

The following variables of gallbladder emptying were evaluated immediately (time 0) and every 15 min after the test meal until 90 min : minimal residual volume

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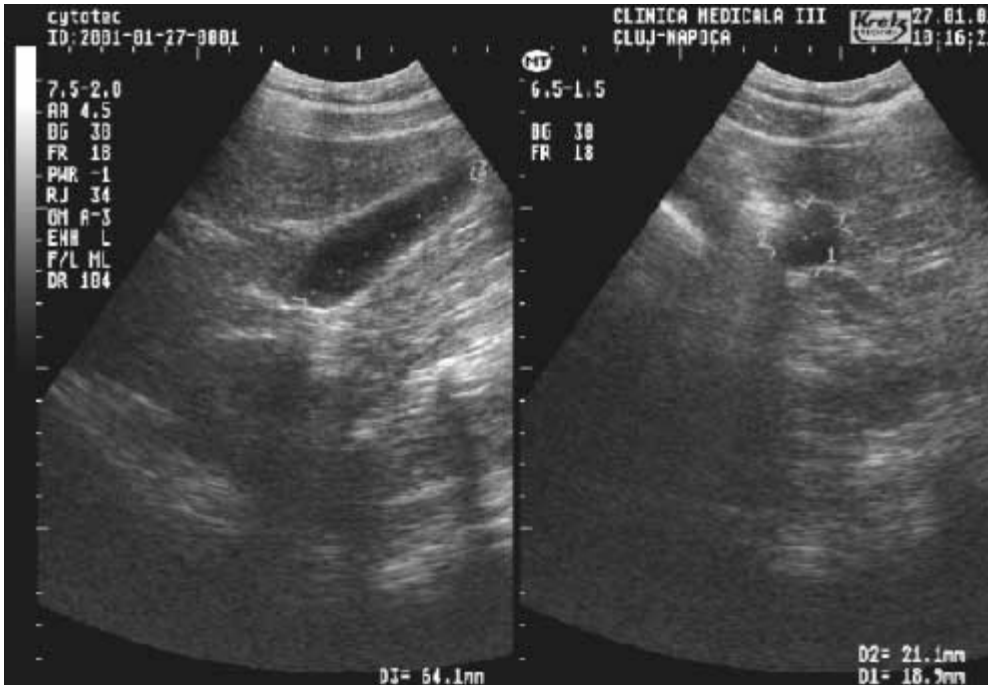

Fig. 1. — Gallbladder volume assessment using the conventional 2D equipment

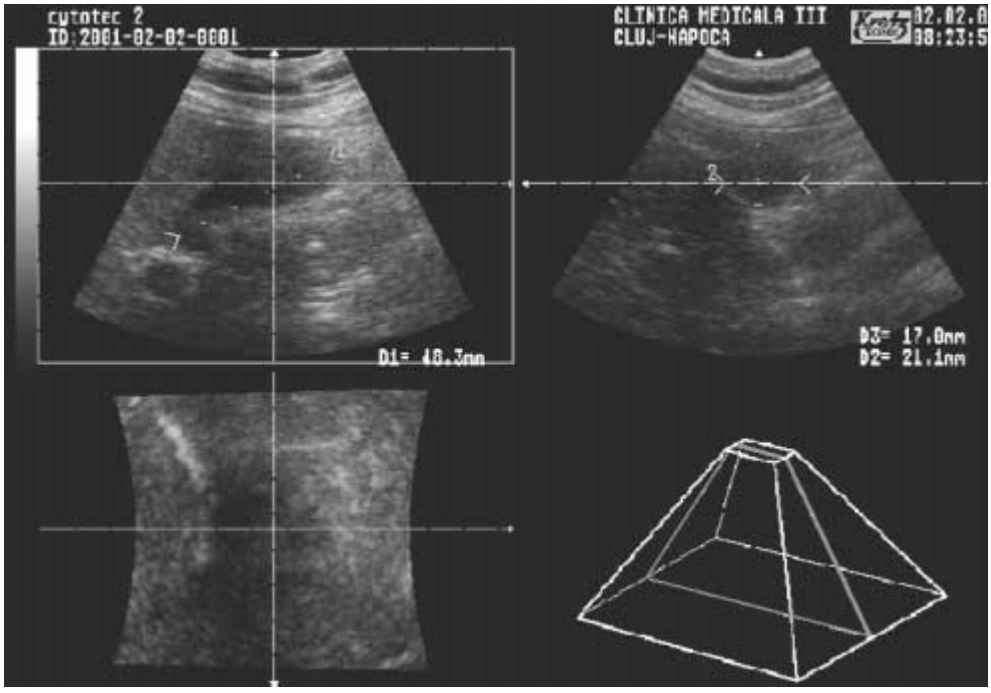

Fig. 2. — Gallbladder volume assessment after the 3D ultrasound reconstruction of the gallbladder

(RV = smallest volume after the meal), ejection fraction (FV-RV/FV x 100), area under emptying curve (AUC = % of FV at 90 min), and half contraction time (T/2) of the gallbladder.

Ultrasound evaluation of gallbladder emptying was performed in each subject on three different days : day 1, without any drug (control group), day 2, after 200 mg Misoprostol (M200 group) and day 3, after 400 mg Misoprostol (M400 group). Misoprostol (Cytotec ; Searle, Chicago, IL) was administered as a single oral dose 60 min before the test meal. The ultrasound examiner was blinded for the study regarding the medication used by the subjects.

Analysis

Gallbladder volumes were expressed as absolute values (cm^3). Data are expressed as mean ± SD. Differences between groups were analyzed using the

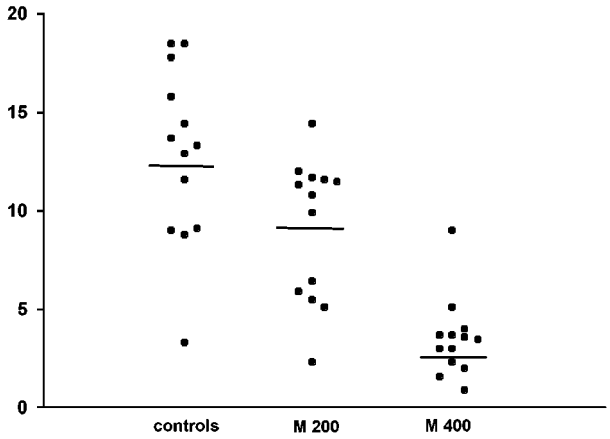

Fig. 3. — The gallbladder fasting volumes (FV) in the three studied groups.

Table I. — **Variables of gallbladder motor function after a mixed meal in controls and after oral administration of misoprostol 200 mg (M200) and 400 mg (M400) before the mixed meal**

	Controls	M200	M400
FV (ml)	12.8 ± 4.4	9.1 ± 3.6*	5.4 ± 2.6**
RV (ml)	3.5 ± 1.7	3.3 ± 1.9	3.1 ± 1.1
Ejection fraction (%)	70.5 ± 17.3	69.2 ± 15.2	53.5 ± 12.7#
AUC (%)	54.4 ± 18.6	59.9 ± 14.5	73 ± 12.9#
T/2 (min)	17.3 ± 9	22.7 ± 14.9	27.4 ± 14.7

● $p < 0.05$ vs controls ; ** $p < 0.01$ vs controls ; # $p < 0.02$ vs. M200 and controls.

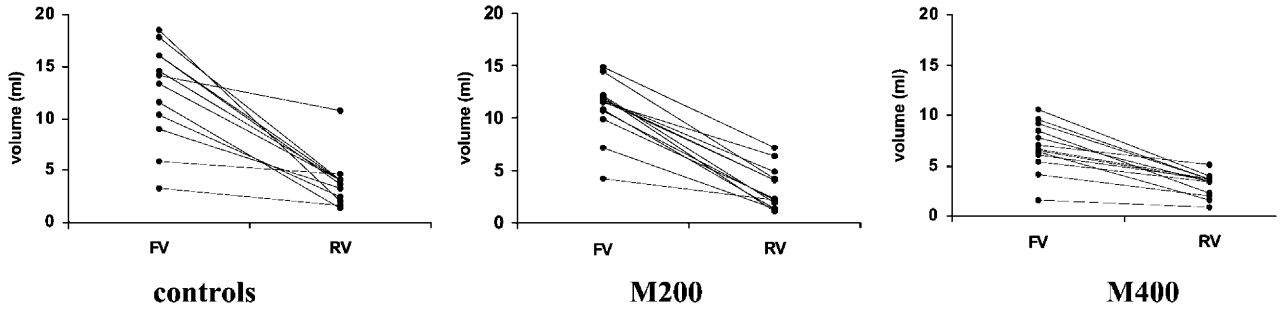

Fig. 4. — The gallbladder volume changes induced by the mixed meal : FV = fasting volume ; RV = residual volume

two-tailed Student's t test for paired observations, with statistical significance set at the $p < 0.05$ level.

Results

Measurements of gallbladder diameters using the 3D reconstruction of the gallbladder were used to evaluate Misoprostol effects in our subjects.

Effect of Misoprostol on fasting gallbladder volume

Gallbladder FV decreased significantly after Misoprostol administration : from 12.8 ± 4.4 ml (controls) to 9.1 ± 3.6 ml (M200) ($0.02 > p < 0.05$) and to 5.4 ± 2.6 ml (M400) ($0.001 > p < 0.01$ vs controls ; $0.02 > p < 0.05$ vs M200) (Fig. 3).

Effect of Misoprostol on gallbladder emptying

The test meal induced gallbladder emptying in all three studied groups (Fig. 4).

In the M200 group, the emptying variables (RV, ejection fraction, AUC and T/2) were similar to those in controls (Table I).

In the M400 group, RV was similar to the RV in controls and M200 group, but the ejection fraction was lower and the AUC was larger (Table I).

The sequential changes in the gallbladder volume could be represented as a monoexponential process after the test meal between time 0 and 60 min (Fig. 5). The slopes of the emptying curves started from different postprandial gallbladder volumes and were different in the three groups only during the first 30 minutes after the test meal. Afterwards, the emptying curves ran almost parallel in all groups.

Adverse effects of Misoprostol

Three of the subjects developed abdominal cramping (in one followed by a loose stool) within 30 minutes after administration of 200 mg Misoprostol. Five of the subjects developed abdominal cramping after the 400 mg dose (all subjects who experienced pain after the 200 mg dose, repeated the pain, but it was less severe). In one of the female subjects, a mild uterine haemorrhage occurred after the 400 mg dose.

Discussion

Bennett *et al.* (1977) identified prostaglandins E and F in human gastric and intestinal mucosa (9). Although there is some direct and indirect evidence for a role of prostaglandins in the control of gastrointestinal tract function, the physiological importance of endogenous prostaglandins is still unclear (10-14).

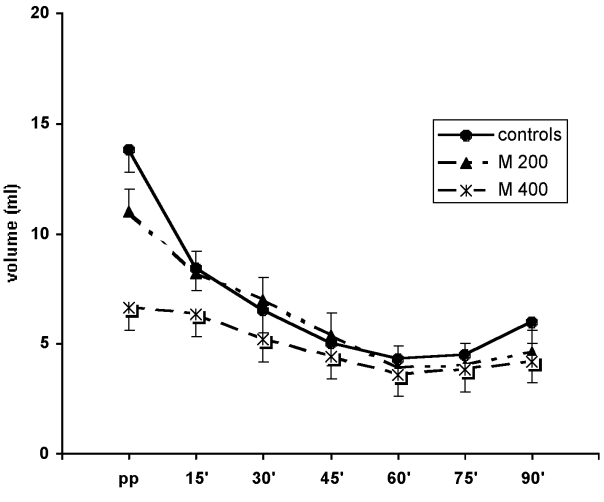

Fig. 5. — The emptying curves of the gallbladder after the test meal in the three studied groups : pp = postprandial volume (immediately after meal ingestion, time 0).

Misoprostol was the first analogue of prostaglandin E1, to be commercially available. Its most frequently reported adverse effect was diarrhoea, which appeared to be dose-related. Diarrhoea was explained by an increased fluid and bicarbonate secretion induced by cAMP stimulation through prostaglandins, but it could be also due to the prokinetic effect of prostaglandins. Animal studies suggested that prostaglandins may initiate a giant migrating complex pattern and increase colonic propulsive activity (15). Misoprostol has proved, in a small series of patients, to be effective for the treatment of chronic refractory constipation, due to its effect on colonic motility (16).

Prostaglandins' effects on the gallbladder were mainly studied regarding mucus production during gallstone formation, and the effect of indomethacin in the prevention of gallstone formation. Prostaglandins have been shown to influence gallbladder motility, although studies focussed on the effects on gallbladder motility have given contradictory results. In a study performed *in vitro* on human gallbladder muscle strips (4) and in another one *in vivo* (5), prostaglandins stimulated gallbladder motility. This effect was diminished in gallbladders of patients with recent acute cholecystitis (4). In a study *in vitro* performed on gallbladders prelevated from dogs, prostaglandins induced relaxation of the gallbladder muscle (6). This variation in response appeared to be dependent upon the species studied and the type and concentration of prostaglandins used.

Indomethacin, a potent inhibitor of prostaglandin synthesis, decreased resting tone and rythmic contractions of gallbladder muscle strips from patients with acute cholecystitis and also decreased resting gallbladder pressure *in vivo* (17). In contrast, using sonography, indomethacin enhanced gallbladder emptying in response to a test meal in a small group of patients after cholecystolithotomy, but did not influence gallbladder motility in healthy subjects (18). These contradictory effects could be due to the small number of cases, or could be explained in the case when indomethacin also reduces the tone and resistance to flow of the sphincter of Oddi (12).

Misoprostol was shown to be rapidly absorbed and de-esterified to its acid form following oral administration to healthy volunteers. Peak plasma concentrations of free acid are reached in 30 to 60 minutes (13,19). We administered Misoprostol 60 min before the test meal, an interval also used by Roarty *et al.* in their study in humans (15).

We used for evaluating gallbladder emptying the diameters assessed after gallbladder 3D reconstruction, because this allowed measurement in two perfectly perpendicular planes.

Our study in healthy volunteers revealed a strong contraction/emptying of the gallbladder in response to Misoprostol during fasting, which was dose-dependent. These results are in agreement with experimental data (4,5) and with the finding of the relaxing effect of indomethacin upon gallbladder smooth muscle in patients with acute cholecystitis (17). Prostaglandin synthesis is stimulated mainly in diseased gallbladders, which could explain the lack of effect of indomethacin on gallbladder motility found in a small group of healthy subjects (18).

Concerning the postprandial gallbladder emptying after administration of Misoprostol, its amplitude was not changed as compared with controls. The emptying curves in the M400 group were similar with those in the M200 group and in controls after the first 15 minutes postprandially (Fig. 4). The modified emptying parameters (ejection fraction and AUC 90) in the M400 group were due to the significantly smaller fasting volumes (Fig. 2). We concluded that Misoprostol had no influence upon meal-stimulated gallbladder emptying in healthy subjects. The interval of 60 min after the oral administration of Misoprostol could not explain this finding, because in other studies significant changes in intestinal motility occurred at 2 hours following oral administration of Misoprostol (16).

Our data showed that Misoprostol strongly and in a dose-dependent manner augmented the gallbladder emptying during the interdigestive phase in healthy subjects. However, pre-prandial administration of Misoprostol did not influence the normal gallbladder response to a solid-liquid meal.

To the best of our knowledge, no one has reported comparatively the effect of Misoprostol on gallbladder motility during fasting and after meals in healthy subjects. As precipitated gallbladder emptying during the interdigestive phase stimulates intestinal motility, Misoprostol effect on gallbladder motility might contribute to diarrhoea, the drug's most frequent side-effect.

A possible application of the stimulative effect of Misoprostol on gallbladder emptying could be for treating gallbladder stasis in patients with chronic constipation.

Misoprostol has already been successfully used for refractory constipation treatment in a small group of patients (16), and the risk of developing gallstones is greater in patients with gallbladder stasis and and/or slow intestinal transit (20). Although Misoprostol is generally well tolerated, it should not be indicated in women of childbearing age, because it increases uterine contractility.

References

1. WILSON D.E., QUADROS E., RAJAPAKSA T., ADAMS A., NOAR M. Effects of misoprostol on gastric acid and mucus secretion in man. *Dig. Dis. Sci.*, 1986, **31** : 126S-129S.
2. MOORE J.G., ALAZRAKI N., CLAY G.D. Effect of synthetic prostaglandin E_1 analog on gastric emptying of meals in man. *Dig. Dis. Sci.*, 1986, **31** : 16S-20S.
3. KIMBERT D.V., FIELD M., JOHNSON J., HENDERSON A., GERSHON E. Stimulation of intestinal mucosa adenylcyclase by cholera enterotoxin and prostaglandins. *J. Clin. Invest.*, 1971, **50** : 1218-1230.
4. KOTWALL C.A., CLANACHAN A.S., BAIE H.P. Effect of prostaglandins on motility of gallbladders removed from patients with gallstones. *Arch. Surg.*, 1984, **119** : 709-712.
5. WOOD J.R., SAVERYMUTTU S.H., ASHBROOKE A.B., STAMFORD I.F. Effects of various prostanoids on gallbladder muscle. *Adv. Prostaglandin Thromboxane Leukotriene Res.*, 1980, **8** : 1569.
6. MROCZKA J., BAER H.P., SCOTT G.W. Effects of prostaglandins in isolated dog gallbladder and cystic duct. In *Motility of the Digestive Tract*. Edited by Wienbeck M. New York : Raven Press, 1982 : 421-426.
7. DODDS W.J., GROH W.J., DARWEESH R.M.A., LAWSON T.L., KISHK S.M.A., KERN M.K. Sonographic measurement of gallbladder volume. *AJR*, 1985, **145** : 1009-1012.
8. ACALOVSCHI M., DUMITRASCU D.L., CSAKANY I. Gastric and gallbladder emptying of a mixed meal are not coordinated in liver cirrhosis – a simultaneous sonographic study. *Gut*, 1997, **40** : 412-417.
9. BENNETT A., STAMFORD I.F., STOCKLEY H.L. Estimation and characterization of prostaglandins in the human gastrointestinal tract. *Br. J. Pharmacol.*, 1977, **61** : 579-586.
10. BAXTER J.N. Gallbladder emptying. *J. Gastroenterol. Hepatol.*, 1989, **4** : 353-372.
11. TIERNEY S., PITT H.A., LILLEMOE K.D. Physiology and pathophysiology of gallbladder motility. *Surg. Clin. N. Am.*, 1993, **73** : 1267-1290.
12. PATANKAR R., OZMEN M.M., BAILEY I.S., JOHNSON C.D. Gallbladder motility, gallstones and the surgeon. *Dig. Dis. Sci.*, 1995, **40** : 2323-2335.
13. MONK J.P., CLISSOLD S.P. Misoprostol : A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of peptic ulcer disease. *Drugs*, 1987, **33** : 1-30.
14. PANDOLFINO J.E., HOWDEN C.W., KAHRILAS P.J. Motility-modifying agents and management of disorders of gastrointestinal motility. *Gastroenterology*, 2000, **118** : S32-S47.
15. FIORAMONTI J., STAUMONT G., GARCIA-VILLAR L., BUENO L. Effect of sennosides on colonic motility. *Pharmacology*, 1988, **36** : 23-30.
16. ROARTY T.P., WEBER F., SOKYAN I., MC CALLUM R.W. Misoprostol in the treatment of chronic refractory constipation : results of a long-term open label trial. *Aliment Pharmacol. Ther.*, 1997, **11** : 1059-1066.
17. THORNELL E., JANSSON R., SVANVIK J. Indomethacin reduces raised intraluminal gallbladder pressure in acute cholecystitis. *Acta Chir. Scand.*, 1985, **151** : 261-265.
18. O'DONNELL L.J.D., WILSON P., GUEST P. *et al.* : Indomethacin and postprandial gallbladder emptying. *Lancet*, 1992, **339** : 269.
19. WALT R.P. Misoprostol for the treatment of peptic ulcer and antiinflammatory-drug-induced gastroduodenal ulceration. *N. Engl. J. Med.*, 1992, **327** : 1575-1580.
20. HEATON K.W., EMMETT P.M., SYMES C.L. *et al.* : An explanation for gallstones in normal-weight women : slow intestinal transit. *Lancet*, 1993, **341** : 8-10.