

The Effect of Metoclopramide in Capsule Enteroscopy

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Abstract Clinical utility of prokinetics in capsule endoscopy (CE) is not clearly established. The objective of this prospective, randomized, single-blind, controlled trial was to determine if metoclopramide is useful in CE by increasing the rate of complete enteroscopy. Ninety-five patients referred for CE were randomized to no metoclopramide (group B, $n = 48$) or 10 mg metoclopramide (group A, $n = 47$). Complete enteroscopy was possible in 38 patients of group A (80.9%) and 37 of group B (77.1%) ($P = 0.422$) with two cases of gastric retention in group B (4.2%; $P = 0.253$). Median gastric transit time was 26 min (1–211) in group A and 28 min (4–200) in group B ($P = 0.511$). Mean small bowel transit time, calculated after excluding 20 patients with incomplete enteroscopy, was similar in both groups (221.2 ± 89 min vs. 256 ± 82.2 min; $P = 0.083$). There were also no differences in the total number of findings (group A 4.5 ± 4.7 ; group B 4.7 ± 3.7 , $P = 0.815$). Administration of 10 mg metoclopramide orally 15 min before capsule ingestion did not significantly increase the rate of total enteroscopies and had no effect on transit times. It also did not modify CE diagnostic yield.

Keywords Capsule endoscopy · Prokinetics · Small bowel endoscopy · Gastroparesis

Background and Aims

After a long period of development [1], wireless capsule endoscopy (CE) was finally presented to the medical community in 2000 [2]. This new endoscope has significant diagnostic capabilities and opened a new chapter in small bowel examination [3]. CE has established indications in obscure gastrointestinal bleeding (OGIB), suspected Crohn's disease and small bowel tumors, surveillance in patients with polyposis syndromes, and suspected or refractory malabsorptive syndromes such as celiac disease [3, 4]. Its diagnostic yield is very good when compared with other diagnostic methods, and has a positive impact on clinical management [5–13]. However, the diagnostic yield depends on the enteroscopy completion rates to the cecum. Incomplete enteroscopy, reported to occur in 15–20% of patients [5, 14], is affected by gastric transit time [15].

Some medical conditions such as diabetes mellitus, functional dyspepsia, vagotomy, hypothyroidism, scleroderma, and some medications (e.g., narcotics) are known to be associated with gastroparesis [16]. Advanced age, diabetes, and inpatient status have been regarded as “high risk” for incomplete capsule studies [15–18]. Prokinetics, by improving gastric emptying and small bowel motility, might be useful, but their use as pre-medication is not widely established [4, 13, 19]. In the study by Selby [15], the use of metoclopramide was associated not only with a higher rate of complete enteroscopy, but also with a lower gastric transit time (GTT) and a combined gastric and small bowel transit time (SBTT) [15]. Mosapride was also useful in CE [20], but erythromycin had no effect on GTT, SBTT, and cecal completion rate [21]. An ideal prokinetic for CE would substantially decrease GTT and increase the rate of total enteroscopy without affecting SBTT or reducing the diagnostic yield.

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The objectives of this prospective, randomized, single blinded, controlled study were to determine whether GTT, SBTT, and the rate of complete enteroscopy in CE were affected by the administration of metoclopramide, and whether the putative acceleration of the transit time interferes with the diagnostic yield of the procedure.

Patients and Methods

Patients

Between November 2006 and November 2007, 100 consecutive patients referred to a single tertiary center for CE, all with negative upper endoscopy and colonoscopy, were assessed for eligibility. Exclusion criteria included age under 18 years, pregnancy, metoclopramide allergy, cardiac pacemakers or other electro-medical devices, swallowing disorders, previous gastric or small bowel surgery, or known enteric strictures. Five patients were excluded because they did not meet the inclusion criteria (previous gastric or small bowel surgery in four and a known Crohn's stricture in one). The reasons for referral of the remaining 95 patients were: OGIB in 62 (overt 34; iron-deficiency anemia 28), suspected Crohn's disease in 15, suspected small bowel lesion in 14, abdominal pain in three, and others in one (Table 1).

These 95 patients were prospectively randomized to no metoclopramide (group B, controls, $n = 48$) or 10 mg metoclopramide (group A, $n = 47$) on the basis of a computer-generated, random-number table.

All patients gave their informed consent to the procedures and all ethical and legal considerations were strictly respected.

CE Procedure

Patients were given standard instructions for the procedure. They consumed only liquids the day before the enteroscopy, and fasted for at least 12 h. No specific bowel preparation was prescribed. Patients allocated to group A received a pill of 10 mg metoclopramide 15 min before swallowing the capsule (SB PillCam; Given Imaging, Yoqneam, Israel). Simethicone was added to the water with which the capsule was ingested. Two hours after ingestion, patients were allowed to drink water and resumed a liquid diet at 4 h. All examinations were performed in a hospital day setting. After 8 h of recording, the images were downloaded to the workstation and were interpreted with RAPID software (Given Imaging) by one of three experienced endoscopists, unaware of the patients' status (metoclopramide vs. control). An interim quality analysis (not published) revealed excellent agreement between

Table 1 Demographic data, reasons for referral, and co-morbidities in the two groups

	Metoclopramide group ($n = 47$)	Control group ($n = 48$)	<i>P</i> -value
Mean age (years)	54.7 \pm 21.1	54.2 \pm 17.4	0.905
Gender (M/F)	19/28	25/23	0.175
Body-mass index (kg/m ²)	24.5 \pm 5.1	24.4 \pm 4.6	0.967
Indication for CE (%)			
OGIB	68.1	62.5	0.361
Overt bleeding	42.6	29.2	0.126
Iron-deficient anemia	25.5	33.3	0.272
Suspected CD	12.7	18.7	0.303
Suspected organic lesion of SB	17.1	12.5	0.370
Abdominal pain	2.1	4.2	0.508
Others	0	2.1	0.505
Co-morbidities (%)			
Arterial hypertension	34	25	0.229
Abdominal surgery	23.4	25	0.523
Osteoarticular disease	17	12.5	0.370
Dyslipidemia	17	10.4	0.262
Immobility	10.6	12.5	0.515
Diabetes mellitus	6.4	8.3	0.512
COPD	2.1	6.3	0.316
Others	44.7	58.3	0.130

COPD chronic obstructive pulmonary disease

these three endoscopists, confirmed by a recent study of the use of a dual camera capsule for small bowel endoscopy (in press). All doubtful images were discussed and analyzed by all three endoscopists.

The following results were considered in each patient: completeness of the enteroscopy (the enteroscopy was considered complete when the image of the cecum was obtained), GTT (time taken from the first gastric image until the first duodenal image), SBTT (time taken from the first duodenal image until the first image of the cecum), and total number of findings (TNF). These findings were classified, in accordance with their relevance to the final diagnosis and following the definition of Costamagna et al. [22], as diagnostic, suspicious, or failed/negative. Diagnostic findings determined final CE diagnostic yield.

The overall quality of small bowel cleanliness was evaluated according to the scale proposed during the 4th International Conference on Capsule Endoscopy by De Franchis et al. [19]. According to this scale, optimum small bowel cleanliness, defined as total absence of bubbles or dark/opaque fluid obscuring the vision, was classified as 0 points.

Gastric retention was assumed when the capsule stayed in the stomach during the entire recording time.

Statistical Analysis

Quantitative data were summarized as mean or median (\pm standard deviation or range) if they were normally or abnormally distributed, respectively, according to the Kolmogorov–Smirnov test. These data were compared using the student *t*-test or a non-parametric test (Mann–Whitney *U* test). Analysis of covariance involving metoclopramide administration as independent variable and GTT, SBTT, and TNF as dependent variables was also performed. Categorical data were presented as a frequency (percentage) and analyzed by use of the Pearson χ^2 -test or Fisher's exact test. A *P*-value of <0.05 indicated statistical significance.

Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) software, version 11.5 (SPSS, Chicago, IL, USA).

Results

Ninety-five patients were included in the study; 47 were randomized into the metoclopramide group (group A) and 48 to the control group (group B). Demographic data, reasons for referral, and co-morbidities are shown in Table 1.

The two groups were similar on the basis of all data including factors already established as capable of affecting GTT and rate of complete examination such as age, diabetes mellitus, ongoing hospitalization, and/or patient immobility.

There were also no differences between groups concerning all medications including insulin, oral antidiabetics, nonsteroidal anti-inflammatory drugs, platelet aggregation inhibitors, antibiotics, proton-pump inhibitors, oral iron supplements, prokinetics, antispasmodics, and narcotics.

The results obtained and statistical data from comparison of the two groups are listed in Table 2. There were two cases of gastric retention in the control group (4.2%) and none in group A ($P = 0.253$). After exclusion of the two patients with gastric retention from the control group, the median GTT was 26 min (range 1–211) in the metoclopramide group and 28 min (range 4–200) in the control group ($P = 0.511$). Twenty patients (nine from Group A and eleven from Group B) were excluded from analysis of SBTT because the enteroscopy was incomplete. These patients were excluded only from this specific analysis because the capsule did not reach the cecum and so it was impossible to determine the SBTT.

Analysis of covariance also revealed no statistically significant differences.

Optimum small bowel preparation (0 points) was recorded in 55.3% of patients in group A and 54.3% in group B ($P = 0.545$).

Table 2 Rate of complete enteroscopy, gastric retention, GTT, SBTT, NTF, and diagnostic yield in the two groups

	Metoclopramide group	Control group	<i>P</i> -value
Complete enteroscopy (%)	80.9	77.1	0.422
Gastric retention (%)	0	4.2	0.253
Median GTT (all patients) (min)	26 (1–211)	31.5 (4–480)	0.324
Median GTT (excluding gastric retention) (min)	26 (1–211)	28 (4–200)	0.511
Mean SBTT (min)	221.2 \pm 89	256 \pm 82.2	0.083
Mean TNF	4.5 \pm 4.7	4.7 \pm 3.7	0.815
Diagnostic yield (%)	68.1	64.6	0.443

A final diagnosis was established in 23 patients in the metoclopramide group (48.9%) and 19 patients in the control group (39.6%; $P = 0.239$). Suspicious findings were found for nine patients in group A (19.1%) and twelve patients (25%) in group B ($P = 0.331$).

There were no cases of unnatural expulsion/retention of CE in these 95 patients. No major or minor complications and no side-effects of metoclopramide were reported.

Discussion

In the setting of small bowel disease, the use of CE is widely accepted, but incomplete enteroscopy should be regarded a major drawback of the procedure. We know that CE fails to reach the cecum in 15–20% of the procedures [5, 14], but higher rates of incomplete enteroscopy have been reported [23]. Gastric retention and delayed gastric emptying are associated with failure of the capsule to reach the colon [15, 16].

Some methods can be used to reduce GTT, for example positioning the patient in right lateral decubitus, placement of capsule in duodenum using an upper endoscope, and increasing battery lifetime. However, increased cost and/or inconvenience to the patients are associated with these procedures. In these circumstances, prokinetics should be useful in CE [19], but several years after the introduction of CE in clinical practice their use is not consensual and has not been systematically recommended [12].

Capsule endoscopy was introduced in our unit in 2001 and we used metoclopramide as a standard pre-medication. However, our complete enteroscopy rate was no better than those recorded by groups that did not use prokinetics.

There are few prospective full papers about prokinetics in CE [13]. Wei et al. [20] demonstrated the efficacy of mosapride. In contrast, Caddy et al. [21] demonstrated that the motilin agonist erythromycin had no effect on GTT, SBTT, or the completion rate of CE examination, although

Leung et al. [24], in a retrospective trial, reported that erythromycin reduces GTT but not SBTT.

Metoclopramide is a dopamine D₂ receptor antagonist, very efficient in treatment of stomach and small bowel motility disorders, including gastroparesis related to diabetes, prior vagotomy, and prior partial gastrectomy [25, 26]. The standard dose is 10–20 mg orally or intravenously, three or four times a day [26]. This prokinetic relaxes the pyloric sphincter and simultaneously intensifies the tonus and amplitude of contractions in the antrum. Effects of metoclopramide in gastrointestinal motility may reach the sigmoid colon and high-amplitude peristaltic waves are observed over the total length of duodenum [27]. It has a rapid and good oral absorption, with mean bioavailability of 77%, a peak plasma concentration at 56 min and a half-life of 5 h [28]. It has a high safety profile even at an oral dose of 20 mg [29] and is readily available and inexpensive.

Selby [15] found that metoclopramide increases the likelihood of complete small-bowel examination in patients undergoing CE. His study included a large number of patients but was not randomized. In our randomized, prospective, single-blind study we found that 10 mg oral metoclopramide taken 15 min before ingestion of the capsule did not increase the rate of complete enteroscopy and did not interfere with GTT and SBTT. In agreement with Selby [15], the TNF and the diagnostic yield were similar in both groups, an expected result because of the absence of interference with SBTT. It is important to notice that in our study the patients were not submitted to any specific bowel preparation, a potential misleading factor because some bowel-cleaning solutions could positively affect intestinal peristalsis, and that the two groups were similar with regard to different variables that might affect results from the study. To address the particular problem of whether the acceleration of transit times by prokinetics might increase the number of lesions missed by the capsule we decided to use the number of all findings independently of their relevance. There were no differences between groups and metoclopramide does not seem to improve or impair diagnostic yield in CE.

Before assuming metoclopramide is useless in CE, it is important to say that we used a single dose of 10 mg whereas some authors propose that a higher oral dose of 30 mg should be investigated [25]. Along with the dose, and given the known pharmacokinetic characteristics of this drug (peak plasma concentration after 56 min), the interval time of only 15 min between administration of metoclopramide and ingestion of the capsule is probably not sufficient and also justifies further evaluation. A longer interval time (45 min–1 h) could eventually be more efficacious.

Metoclopramide might also be effective in some patients groups, for example diabetics, older patients, and those

with limited mobility. Larger doses of this prokinetic, or intravenous administration, might be needed in these patients.

Two cases of gastric retention occurred in controls and none in the metoclopramide group. Only with a much larger sample would it be possible to determine whether this prokinetic can prevent gastric retention. Another field of investigation is the potential use of metoclopramide administered intravenously when, with real time view, we detect a delayed gastric emptying of the capsule.

In summary, the results of our study suggest that the use of 10 mg metoclopramide administered orally 15 min before capsule ingestion does not increase the rate of total enteroscopy and has no effect on transit times and so, probably, is not useful for CE. Studies involving a larger number of patients, administration of larger doses of metoclopramide (20–30 mg), a longer interval time (1 h) between administration of the prokinetic and the ingestion of the capsule, and intravenous use in cases of documented gastric retention must take place to definitively determine the importance of this prokinetic for capsule endoscopy.

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References

1. Meron G. The development of the swallowable video capsule (M2A). *Gastrointest Endosc.* 2000;52:817–819. doi:10.1067/mge.2000.110204.
2. Iddan G, Meron G, Glukhovskiy A, Swain P. Wireless capsule endoscopy. *Nature.* 2000;405:417. doi:10.1038/35013140.
3. Pennazio M. Capsule endoscopy: where are we after 6 years of clinical use? *Dig Liver Dis.* 2006;38:867–878. doi:10.1016/j.dld.2006.09.007.
4. Gay G, Delvaux M, Fassler I. Indications of CE. In: Gay G, ed. *Capsule Endoscopy of the Small Bowel*. Nancy: ALN editions; 2006:24–63.
5. Rondonotti E, Villa F, Mulder CJ, Jacobs M, De Franchis R. Small bowel capsule endoscopy in 2007: indications, risks and limitations. *World J Gastroenterol.* 2007;13:6140–6149. doi:10.3748/wjg.13.6140.
6. American Society for Gastrointestinal Endoscopy. ASGE technology status evaluation report: wireless capsule endoscopy. *Gastrointest Endosc.* 2006;63:539–545. doi:10.1016/j.gie.2006.01.014.
7. Pennazio M, Eisen G, Goldfarb N. ICCE consensus for obscure gastrointestinal bleeding. *Endoscopy.* 2005;37:1046–1050. doi:10.1055/s-2005-870319.
8. Kornbluth A, Colombel JF, Leighton JA, Loftus E. ICCE consensus for inflammatory bowel disease. *Endoscopy.* 2005;37:1051–1054. doi:10.1055/s-2005-870315.
9. Pennazio M, Santucci R, Rondonotti E, et al. Outcome of patients with obscure gastrointestinal bleeding after capsule endoscopy: report of 100 consecutive cases. *Gastroenterology.* 2004;126:643–653. doi:10.1053/j.gastro.2003.11.057.
10. Triester SL, Leighton JA, Leontiadis GI, et al. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with obscure gastrointestinal bleeding. *Am*

- J Gastroenterol.* 2005;100:2407–2418. doi:[10.1111/j.1572-0241.2005.00274.x](https://doi.org/10.1111/j.1572-0241.2005.00274.x).
11. Triester SL, Leighton JA, Leontiadis GI, et al. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with non-stricturing small bowel Crohn's disease. *Am J Gastroenterol.* 2006;101:954–964. doi:[10.1111/j.1572-0241.2006.00506.x](https://doi.org/10.1111/j.1572-0241.2006.00506.x).
 12. Gupta R, Reddy DN. Capsule endoscopy: current status in obscure gastrointestinal bleeding. *World J Gastroenterol.* 2007;13:4551–4553.
 13. Mergener K, Ponchon T, Granek I, et al. Consensus statements for small-bowel capsule endoscopy, 2006/2007. *Endoscopy.* 2007;39:895–909. doi:[10.1055/s-2007-966930](https://doi.org/10.1055/s-2007-966930).
 14. Triantafyllou K, Kalantzis C, Papadopoulos AA, et al. Video-capsule endoscopy gastric and small bowel time and completeness of the examination in patients with diabetes mellitus. *Dig Liver Dis.* 2007;39:575–580. doi:[10.1016/j.dld.2007.01.024](https://doi.org/10.1016/j.dld.2007.01.024).
 15. Selby W. Complete small-bowel transit in patients undergoing capsule endoscopy: determining factors and improvement with metoclopramide. *Gastrointest Endosc.* 2005;61:80–85. doi:[10.1016/S0016-5107\(04\)02462-9](https://doi.org/10.1016/S0016-5107(04)02462-9).
 16. Ben-Soussan E, Savoye G, Antonietti M, Ramirez S, Lerebours E, Ducrotte P. Factors that affect gastric passage of video capsule. *Gastrointest Endosc.* 2005;62:785–790. doi:[10.1016/j.gie.2005.07.040](https://doi.org/10.1016/j.gie.2005.07.040).
 17. Fireman Z, Paz D, Kopelman Y. Capsule endoscopy: improving transit time and image view. *World J Gastroenterol.* 2005;11: 5863–5866.
 18. Enns R. Transit times in capsule endoscopy: Are all patients the same? *Dig Liver Dis.* 2007;39:581–583. doi:[10.1016/j.dld.2007.03.002](https://doi.org/10.1016/j.dld.2007.03.002).
 19. De Franchis R, Avgerinos A, Barkin J, Cave D, Filoche B. ICCE consensus for bowel preparation and prokinetics. *Endoscopy.* 2005;37:1040–1045. doi:[10.1055/s-2005-870327](https://doi.org/10.1055/s-2005-870327).
 20. Wei W, Ge ZZ, Lu H, Gao YJ, Hu YB, Xiao SD. Effect of mosapride on gastrointestinal transit time and diagnostic yield of capsule endoscopy. *J Gastroenterol Hepatol.* 2007;22:1605–1608. doi:[10.1111/j.1440-1746.2007.05064.x](https://doi.org/10.1111/j.1440-1746.2007.05064.x).
 21. Caddy GR, Moran L, Chong AK, Miller AM, Taylor AC, Desmond PV. The effect of erythromycin on video capsule endoscopy intestinal-transit time. *Gastrointest Endosc.* 2006; 63:262–266. doi:[10.1016/j.gie.2005.07.043](https://doi.org/10.1016/j.gie.2005.07.043).
 22. Costamagna G, Shah SK, Riccioni ME, et al. A prospective trial comparing small bowel radiographs and video capsule endoscopy for suspected small bowel disease. *Gastroenterology.* 2002;123: 999–1005. doi:[10.1053/gast.2002.35988](https://doi.org/10.1053/gast.2002.35988).
 23. Rastogi A, Schoen RE, Slivka A. Diagnostic yield and clinical outcomes of capsule endoscopy. *Gastrointest Endosc.* 2004;6:959–964. doi:[10.1016/S0016-5107\(04\)02226-6](https://doi.org/10.1016/S0016-5107(04)02226-6).
 24. Leung WK, Chan FK, Fung SS, Wong MI, Sung JJ. Effect of oral erythromycin on gastric and small bowel transit time of capsule endoscopy. *World J Gastroenterol.* 2005;11:4865–4868.
 25. Schwarzberg MN. Pro-kinetic medications as aids in imaging the small bowel by video-capsule. *Med Hypotheses.* 2005;64: 602–607. doi:[10.1016/j.mehy.2004.07.031](https://doi.org/10.1016/j.mehy.2004.07.031).
 26. Malagelada JR, Malagelada C. Nausea and vomiting. In: Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 8th edn Elsevier; 2006: 143–158.
 27. Eisner M. Effect of metoclopramide on gastrointestinal motility in man. *Am J Dig Dis.* 1971;16:409–419. doi:[10.1007/BF02235085](https://doi.org/10.1007/BF02235085).
 28. Ross-Lee LM, Eadie MJ, Hooper WD, Bochner F. Single-dose pharmacokinetics of metoclopramide. *Eur J Clin Pharmacol.* 1981;20:465–471. doi:[10.1007/BF00542101](https://doi.org/10.1007/BF00542101).
 29. Kreel L. The use of metoclopramide in the barium meal and follow-through examination. *Br J Radiol.* 1970;43:31–35.