Polyethylene glycol and prevalence of colorectal adenomas

Population-based study of 1165 patients undergoing colonoscopy

Etienne DORVAL (1), Jean Marie JANKOWSKI (2), Association Gastro 37 (2), Jean-Pierre BARBIEUX (1), Jérôme VIGUIER (1), Philippe BERTRAND (1), Brigitte BRONDIN (1), Philippe BOUGNOUX (1), Denis E. CORPET (3)

Gastroentérologie, Hôpital Trousseau, CHRU de Tours ; (2) Cabinet Médical, 11, rue Georges Sand, Tours ; (3) UMR ENVT-INRA Xenobiotiques, Toulouse.

SUMMARY

Background and aim — Dietary polyethylene glycol (PEG) is extraordinarily potent in the chemoprevention of experimental colon carcinogenesis. PEG is used to treat constipation in France and in the USA. French laxatives include Forlax® (PEG4000), Movicol® and Transipeg® (PEG3350), and Idrocol® (pluronic F68). This study tests the hypothesis that use of a PEG-based laxative might reduce the prevalence of colorectal tumors.

Methods — In this population-based study, consecutive patients attending for routine total colonoscopy were enrolled during four months by the gastroenterologists of Indre-et-Loire. They were asked if they had previously taken a laxative or a NSAID. Age, gender, previous polyps, family history of colorectal cancer, constipation, digestive symptoms were also recorded. Tumors found during colonoscopy were categorized histologically.

Results — Records from 1165 patients fulfilled the inclusion criteria, 607 women and 498 men, mean age 58.3. Among those, 813 had no tumor, 329 had adenomas, and 23 had carcinomas. In a univariate analysis, older age, male gender, lack of digestive symptom, and previous polyps were more common in patients with colorectal tumors. In contrast, previous Forlax® intake was more common in tumor-free patients (odds ratio (OR) any use/no use, 0.52; 95% confidence interval, 0.27-0.94). More people used Forlax®, which contains a higher dose of PEG than the other PEG-laxatives, whose ORs were smaller than one, but did not reach significance. In multivariate analysis, older age and male gender were associated with higher risk, and NSAIDs use with lower risk, of colorectal tumors.

Conclusion — Forlax® users had a halved risk of colorectal tumors in univariate analysis, which suggests that PEG may prevent carcinogenesis.

RÉSUMÉ

Polyéthylène Glycol et prévalence des adénomes colorectaux : étude de population chez 1165 patients explorés par coloscopie

Etienne DORVAL, Jean Marie JANKOWSKI, Association Gastro 37, Jean-Pierre BARBIEUX, Jérôme VIGUIER, Philippe BERTRAND, Brigitte BRONDIN, Philippe BOUGNOUX, Denis E. CORPET

Introduction — Le polyéthylène glycol (PEG) administré par voie orale prévient de façon très puissante la cancérogénèse colique expérimentale. Le PEG est utilisé dans le traitement de la constipation en France et aux USA. En France, le PEG est commercialisé sous les noms de Forlax® (PEG4000), Movicol® et Transipeg® (PEG3350), et Idrocol® (pluronic F68). Cette étude a testé l'hypothèse que l'utilisation de l'un de ces PEG pouvait réduire la prévalence des néoplasies colorectales.

Patients et méthodes — Dans cette étude de population tous les malades ayant eu une coloscopie totale ont été inclus sur une période de 4 mois par les gastroentérologues de l'Indre et Loire. Les malades ont été interrogés par questionnaire sur la prise de laxatifs ou d'anti-inflammatoires non stéroïdiens. Âge, sexe, antécédents de polypes ou de tumeurs, antécédents familiaux de cancer colorectal, constipation et autres symptômes digestifs ont été également notés. Les lésions découvertes en coloscopie ont été classées selon l'examen histologique des prélèvements.

Résultats — Au cours des 4 mois, 1165 malades remplissant les critères d'inclusion ont été inclus, 607 femmes et 498 hommes âgés de 58.3 ans en moyenne. Parmi eux, 813 ne présentaient pas de tumeur et 352 une néoplasie colique (329 avaient au moins un adénome et 23 un adénocarcinome). En analyse univariée, l'âge, le sexe masculin, l'absence de symptôme digestif et les antécédents de polypes coliques étaient plus fréquents chez les malades avec néoplasie colique. En revanche, la prise de Forlax®, qui était le PEG le plus utilisé et un des plus fortement dosés, était plus fréquente chez les malades indemnes (OR = 0.52 ; IC 95 % : 0.27-0.94). En analyse multivariée, l'âge et le sexe masculin étaient associés à un risque plus élevé de néoplasie colique tandis que la prise d'AINS était associée à une diminution de ce risque.

Conclusion — Les malades utilisant du PEG (Forlax®) ont un risque de néoplasie colique diminué de moitié en analyse univariée, suggérant que le PEG pourrait prévenir la carcinogenèse colique.

Introduction

Colorectal cancer is the leading cause of cancer death in North-American and European non-smokers. In spite of a very active clinical research, the five-year survival is still close to 50%. Prevention strategies based on epidemiological data and preclinical studies led to large-scale randomized studies. Multiple intervention trials with wheat bran, beta-carotene, ursodeoxycholic acid, folic acid or vitamins C and/or E supplements, and fat reduction, did not prevent polyp recurrence. By contrast, calcium, sulindac, or aspirin did bring a significant benefice, although a modest one. These successful interventions reduced polyp recurrence by 15 to 35% [1-5]. New chemopreventive agents are thus needed.

Polyethylene glycol 4000 (PEG), or macrogol, is a watersoluble polymer which is not absorbed or metabolized after ingestion, and has no known toxicity. It is given orally for the treatment of chronic constipation [6-14], and was permitted for use for this indication in France in 1996, and in the USA and Canada in 2002. PEG has been shown in several animal models to reduce aberrant crypt foci and to prevent azoxymethaneinduced colorectal cancer, with a striking efficacy [15-17]. Against azoxy-methane-induced tumors in rats, only celecoxib is more effective than PEG [18]. No agent is more potent than PEG on aberrant crypts foci, but pluronic F68, a PEG-like block-polymer [19]. Conflicting results were observed in Min mice, a model for patients with Familial Adenomatous Polyposis: PEG treatment reduced the polyp yield in one study, but increased it in another one [20, 21]. PEG inhibits proliferation, and causes apoptosis, in human HT29 colon cancer cells in vitro [22, 23]. PEG might thus be a major chemopreventive agent, but its effects on colonic carcinogenesis in human have not been reported. Before a prevention trial is set up, it is of paramount importance to get observation data, particularly to rule out the possible adverse effect suggested by one of the Min mice studies [24].

The aim of this pilot population study was to compare the prevalence of adenoma and colon cancer with prescription of PEG at usual therapeutic doses for the treatment of chronic constipation

Patients and methods

All patients undergoing colonoscopy in the Indre-et-Loire region, performed by a hospital-based or private gastroenterologist (Association Gastro 37) between October 2001 and January 2002 were asked to complete a questionnaire. Gender, age, reason for colonoscopy (control after polyp or can-

cer treatment, symptoms of gastrointestinal disorder, colon cancer screening), personal and familial history of colonic neoplasias, frequency of stools, presence of gastrointestinal symptoms
and ingestion of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) were recorded for each patient. Treatment with PEG for constipation was also investigated by the following questions: "Are you constipated and if so what treatment are you receiving?", "Which drugs are you taking currently?", "Have you ever taken Forlax®, Movicol®, Transipeg® or Idrocol®?". All the parameters were compared with the results of the colonoscopy, defined as "positive" by the presence of adenoma and/or cancer confirmed by histology examination. Patients who refused to fill in the questionnaire, or whose colonoscopy was incomplete or positive but without histological confirmation, were excluded from the study.

Having established in a preliminary study that there was a prevalence of PEG treatment in about 15%, and a prevalence of positive colonoscopy results, in about 20% of patients undergoing colonoscopy (unpublished personal results), it was decided that 817 patients were required to reveal 50% reduction in risk of detection of adenoma or cancer related to PEG ingestion, with a power of 0.80 and alpha risk of 0.05.

Results

The records of 1165 patients who underwent total colonoscopy and who replied to the questionnaire were studied. They were 498 men and 607 women, mean age 58.3 years, whose characteristics are summarized in table I. The prevalence of positive colonoscopy was 30%: twenty three (2%) colonoscopies revealed cancer and 329 (28%) revealed adenoma. Constipation and/or fewer than 3 stools passed per week were reported by 35% women and 15% men (gender difference, $P < 0.0001$), unrelated to colonoscopy results. One hundred thirty-nine (12%) of the patients had received PEG (17.4% of women and 5.5% of men, $P < 0.0001$). On univariate analysis (table I) male gender, older age, family history of colorectal polyp or cancer, prior colorectal polyp or cancer, and lack of digestive symptoms were significantly more frequent in patients with positive colonoscopy than those without.

By contrast, ingestion of Forlax® was more frequent in patients with no lesion and was associated with a halved risk of positive colonoscopy (table II). The use of the other PEG-laxatives, of aspirin, and of any NSAID, was associated with non significant reduced risk.

In multivariate analysis, older age (OR = 1.04 per year, $P = 0.0001$) and male gender (OR = 1.6, $P = 0.001$) remained associated with higher risk, and NSAIDs use with lower risk (OR = 0.58, $P = 0.015$), of colorectal tumors. No other factor, including previous polyp or cancer, constipation, fiber intake, aspirin, Forlax® or any PEG-based laxative use, did show a significant effect in the multivariate logistic regression analysis.

Discussion

Previous Forlax® intake was more common in tumor-free patients and its use was associated with a halved risk of colorectal tumors. In this pilot study, the results show for the first time that PEG based Forlax® ingestion was associated with 48% reduction in risk of finding adenoma or cancer on complete colonoscopy. This effect seems similar to the effects reported with NSAIDs and aspirin in epidemiological [25-27] and intervention studies [2-5], but no previous study reported a direct comparison of PEG and NSAIDs. In this population, Forlax® use was more protective than aspirin use. The significant association observed for Forlax® on univariate analysis was not observed for other PEG-based laxatives, nor for the entire group of patients who admitted taking PEG. Although non-significant, all the ORs for PEG-based laxatives were smaller than one, which rules out that PEG could increase the tumor growth, as suggested by one study in Min mice with *APC* mutation [21, 28].

Table I. – Characteristics of subjects participating in the study.
Caractéristiques des sujets participants à l'étude.

Factor	Patients with negative colonoscopy	Patients with positive colonoscopy	OR	P
No. of patients	813	352		
Mean age±SD (year)	56 ±14	63±11		0.001
Gender (males, %)	41.8	53.1	1.58	< 0.001
Prior adenoma or cancer,%	23.1	32.1	1.36	< 0002
Family history of adenoma or cancer,%	41.9	48.0	1.19	< 0.06
Digestive symptoms,%	69.2	61.6	1,40	0.02
Constipated,%	24.8	24.4	0.98	NS

Notes to table I: OR, odds ratio; P, significance by the Fisher exact's test; SD, standard deviation; NS, not significant.

The mechanism by which PEG can prevent carcinogenesis is not known, because PEG does not belong to a class of known preventive agents. Speculated mechanisms include (i) dilution of promoting compounds in the gut lumen due to PEG bulking properties [15], (ii) protection of epithelia from irritation and abrasion, by PEG lubricating, coating, and sealing properties [19], (iii) removal of cancer cells from tumors by apoptosis. Results from *in vitro* studies and in vivo observations suggest the removal of cancer cells from tumors be the major mechanism of PEG protection [22, 23, 29].

The study was based on a patient-completed questionnaire. This method is easy to set up and it quickly yielded PEG ingestion data. It is unlikely that non-users did report PEG usage by mistake, but likely that some PEG users forgot to report PEG usage. On the other hand, data from the questionnaire were not precise, and were not validated. Particularly, this survey did not yield reliable information regarding the duration, quantity, regularity or timing of PEG ingestion. Some patients took PEG intermittently, some had ceased treatment as much as several months before the study, or had only recently started, suggesting that the number of patients "really" exposed to PEG, i.e. regularly and for a long period of time, was overestimated. These limitations of the questionnaire could have led to misestimate the protective effect of PEG-based laxatives.

The absence of significant reduction in risk with brands of PEG other than Forlax® was possibly related to a lack of power in the study. Indeed, Forlax® was the most frequently used laxative in this study. In addition, PEG dose varies from one brand to another, and appears to be among the highest in Forlax®. This too may explain the protective effect afforded by Forlax® alone. Last, Idrocol® does not contain PEG, but a PEG-like block polymer, pluronic F68. In animal models, pluronic is five times more potent than PEG against colon carcinogenesis [19], and here, all Idrocol® users were tumor-free (table II).

Table II. – Association of drug use (questionnaire data) with adenoma or cancer found at colonoscopy (histological data) among 1165 patients.

Association entre l'utilisation de médicaments (données issues des questionnaires) et la présence d'adénome ou de cancers détectés lors de la colonoscopie (données histologiques), chez 1165 malades.

| Colonoscopy | Number of patients | | | | | | |
| | negative | | positive | | | | |
Drug use	Users	Non users	Users	Non Users	OR	95% CI	P
Forlax®	60	753	14	338	0.52	0.28-0.94	0.03
Movicol®	46	767	19	333	0.95	0.55-1.6	NS
Transipeg®	27	786	11	341	0.94	0.46-1.9	NS
Idrocol®	6	807	0	352	0.18	0.01-3.1	0.11
Any PEG laxative	100	713	39	313	0.89	0.60-1.3	NS
Aspirin	57	756	19	333	0.76	0.44-1.3	NS
Any NSAID	96	717	34	318	0.80	0.53-1.2	NS

Note to table II: OR, odds ratio; CI, confidence interval; P, significance by the Fisher exact's test; NS, Not Significant; PEG, polyethylene glycol; NSAID, non steroidal anti-inflammatory drug. Number of users taking "Any PEG laxative" is smaller than the sum of above data, because some constipated patients used more than one laxative.

On multivariate analysis, the reduction in risk in Forlax® or PEG users was not significant, perhaps due to an inclusion bias related to the recruitment method. The patients who were included were selected because they were undergoing colonoscopy for follow-up or detection of lesions and not because they were taking PEG. The risk of a positive result on colonoscopy is lower in women than in men in the general population, as shown here [30]. Functional constipation (and thus taking a laxative such as PEG) is, however, more common in women, as also shown here [31, 32]. Finally, the role of constipation in cancer of the colon suggested by certain epidemiological studies remains controversial and was not confirmed in this study, but might have been masked by PEG use [33, 34].

On multivariate analysis NSAIDs use was associated with a significant reduction in the risk of adenoma and cancer, in agreement with previous reports [14-16]. The protective effects of NSAIDs, and the bias suggested above, may have reduced the magnitude of PEG effect in this study. Despite these factors, a significantly reduced risk of finding adenoma or cancer of the colon was observed with Forlax® on univariate analysis. This suggests that the antitumoral effects of PEG in a controlled prospective study of a homogeneous high risk population might in fact be greater than that observed with aspirin and NSAIDs in similar experimental conditions [17-19]. Indeed, rat studies show that the magnitude of PEG chemopreventive effect is usually greater than that of other known chemopreventive agents such as NSAIDs [18].

In conclusion, this pilot study in a population at high risk of colonic lesions shows that it was 50% less likely that patients with adenoma or cancer of the colon would receive Forlax® for constipation, a PEG-based laxative, suggesting a protective role of that PEG affords protection: an intervention trial is needed to prove the link. The intensity of the effect, which was at least comparable to that of aspirin [19], and the good tolerance of PEG [1-9], suggest that the protective effects of treatment with PEG should be studied in patients at high risk of colonic lesions, whether they are constipated or not.

REFERENCES

1. Baron JA, Beach M, Mandel JS, van Stolk RU, Haile RW, Sandler RS, et al. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. N Engl J Med 1999;340:101-7.

2. Giardiello FM, Yang VW, Hylind LM, Krush AJ, Petersen GM, Trimbath JD, et al. Primary chemoprevention of familial adenomatous polyposis with sulindac. N Engl J Med 2002;346:1054-9.

3. Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, et al. A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med 2003;348:891-9.

4. Sandler RS, Halabi S, Baron JA, Budinger S, Paskett E, Keresztes R, et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. N Engl J Med 2003;348: 883-90.

5. Benamouzig R, Deyra J, Martin A, Girard B, Jullian E, Piednoir B, et al. Daily soluble aspirin and prevention of colorectal adenoma recurrence: one-year results of the APACC trial. Gastroenterology 2003;125:328-36.

6. Pashankar DS, Loening-Baucke V, Bishop WP. Safety of polyethylene glycol 3350 for the treatment of chronic constipation in children. Arch Pediatr Adolesc Med 2003;157:661-4.

7. Chaussade S, Minic M. Comparison of efficacy and safety of two doses of two different polyethylene glycol-based laxatives in the treatment of constipation. Aliment Pharmacol Ther 2003;17:165-72.

8. Loening-Baucke V.Polyethylene glycol without electrolytes for children with constipation and encopresis. J Pediatr Gastroenterol Nutr 2002;34:372-7.

9. Cleveland MV, Flavin DP, Ruben RA, Epstein RM, Clark GE. New polyethylene glycol laxative for treatment of constipation in adults: a randomized, double-blind, placebo-controlled study. South Med J 2001;94:478-81.

10. Corazziari E, Badiali D, Bazzocchi G, Bassotti G, Roselli P, Mastropaolo G, et al. Long term efficacy, safety, and tolerabilitity of low daily doses of isosmotic polyethylene glycol electrolyte balanced solution (PMF-100) in the treatment of functional chronic constipation. Gut 2000;46:522-6.

11. DiPalma JA, DeRidder PH, Orlando RC, Kolts BE, Cleveland MB. A randomized, placebo-controlled, multicenter study of the safety and efficacy of a new polyethylene glycol laxative. Am J Gastroenterol 2000;95:446-50.

12. Attar A, Lemann M, Ferguson A, Halphen M, Boutron MC, Flourie B, et al. Comparison of a low dose polyethylene glycol electrolyte solution with lactulose for treatment of chronic constipation. Gut 1999;44:226-30.

13. Corazziari E, Badiali D, Habib FI, Reboa G, Pitto G, Mazzacca G, et al. Small volume isosmotic polyethylene glycol electrolyte balanced solution (PMF-100) in treatment of chronic nonorganic constipation. Dig Dis Sci 1996;41:1636-42.

14. Couturier D. Comparative study of Forlax and Transipeg in the treatment of functional constipation in the adult. Ann Gastroenterol Hepatol (Paris) 1996;32:135-40.

15. Corpet DE, Parnaud G. Polyethylene-glycol, a potent suppressor of azoxymethane-induced colonic aberrant crypt foci in rats. Carcinogenesis 1999;20:915-8.

16. Corpet DE, Parnaud G, Delverdier M, Peiffer G, Tache S. Consistent and fast inhibition of colon carcinogenesis by polyethylene glycol in mice and rats given various carcinogens. Cancer Res 2000;60:3160-4.

17. Parnaud G, Tache S, Peiffer G, Corpet DE. Polyethylene-glycol suppresses colon cancer and causes dose-dependent regression of azoxymethane-induced aberrant crypt foci in rats. Cancer Res 1999; 59:5143-7.

18. Corpet DE, Tache S. Most effective colon cancer chemopreventive agents in rats: a systematic review of aberrant crypt foci and tumor data, ranked by potency. Nutr Cancer 2002;43:1-21.

19. Parnaud G, Tache S, Peiffer G, Corpet DE. Pluronic F68 block polymer, a very potent suppressor of carcinogenesis in the colon of rats and mice. Br J Cancer 2001;84:90-3.

20. Roy HK, Gulizia J, DiBaise JK, Karolski WJ, Ansari S, Madugula M, et al. Polyethylene glycol inhibits intestinal neoplasia and induces epithelial apoptosis in Apc(min) mice. Cancer Lett 2004;215:35-42.

21. Naigamwalla D, Chia MC, Tran TT, Medline A, Hay K, Gallinger S, et al. Polyethylene glycol 8000 and colon carcinogenesis: inhibition in the F344 rat, promotion in the Min mouse. Cancer Res 2000;60: 6856-8.

22. Parnaud G, Corpet DE, Gamet-Payrastre L. Cytostatic effect of polyethylene glycol on human colonic adenocarcinoma cells. Int J Cancer 2001;92:63-9.

23. Roy HK, DiBaise JK, Black J, Karolski WJ, Ratashak A, Ansari S. Polyethylene glycol induces apoptosis in HT-29 cells: potential mechanism for chemoprevention of colon cancer. FEBS Lett 2001;496:143-6.

24. Corpet DE, Pierre F. Point: From animal models to prevention of colon cancer. Systematic review of chemoprevention in min mice and choice of the model system. Cancer Epidemiol Biomarkers Prev 2003;12:391-400.

25. Reeves MJ, Newcomb PA, Trentham-Dietz A, Storer BE, Remington PL. Nonsteroidal anti-inflammatory drug use and protection against colorectal cancer in women. Cancer Epidemiol Biomarkers Prev 1996;5:955-60.

26. Logan RF, Little J, Hawtin PG, Hardcastle JD. Effect of aspirin and non-steroidal anti-inflammatory drugs on colorectal adenomas: casecontrol study of subjects participating in the Nottingham faecal occult blood screening programme. BMJ 1993;307:285-9.

27. Rahme E, Barkun AN, Toubouti Y, Bardou M. The cyclooxygenase- 2-selective inhibitors rofecoxib and celecoxib prevent colorectal neoplasia occurrence and recurrence. Gastroenterology 2003;125:404-12.

28. Bruce WR. Counterpoint: from animal models to prevention of colon cancer. Cancer Epidemiology Biomarkers & Prevention 2003;12:400-403.

29. Taché S, Parnaud G, Van Beek E, Corpet DE. Polyethylene glycol, unique among laxatives, suppresses aberrant crypt foci, by elimination of cells. Scand J Gastroenterol 2006 (in press).

30. McCashland TM, Brand R, Lyden E, de Garmo P. Gender differences in colorectal polyps and tumors. Am J Gastroenterol 2001;96:882-6.

31. Frexinos J, Denis P, Allemand H, Allouche S, Los F, Bonnelye G. Etude descriptive des symptômes fonctionnels digestifs dans la population générale française. Gastroenterol Clin Biol 1998;22:785-91.

32. Bommelaer G, Dorval E, Denis P, Czernichow P, Frexinos J, Pelc A, et al. Prevalence of irritable bowel syndrome in the French population according to the Rome I criteria. Gastroenterol Clin Biol 2002;26: 1118-23.

33. Jacobs EJ, White E. Constipation, laxative use, and colon cancer among middle-aged adults. Epidemiology 1998;9:385-91.

34. Roberts MC, Millikan RC, Galanko JA, Martin C, Sandler RS. Constipation, laxative use, and colon cancer in a North Carolina population. Am J Gastroenterol 2003;98:857-64