Movicol in treatment of constipation and faecal impaction

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To resolve severe constipation or faecal impaction requires the induction of a large increase in faecal water content that hitherto has only been achieved with enemas. A novel iso-osmotic laxative has been shown to achieve a similar effect from oral dosing.

Constipation is commonly caused by a combination of dietary and emotional factors, poor fluid intake and sedentary lifestyle. It may also be secondary to disease (e.g. multiple sclerosis, Parkinson's disease) or drug treatment (e.g. antidepressants, opiates). The initial management of constipation involves identification and, if possible, elimination of the primary cause, education of the patient in the physiology of defaecation, initiation of a diet adequate in fibre and fluid and advice to take more exercise. Bulk-forming agents, having a more physiological action on the bowel than other groups of laxatives, may serve well in place of adequate dietary fibre (Greenberger et al, 1978).

If the patient does not respond to simple measures, consideration should be given to initiating a short course of a suitable laxative. If constipation is allowed to go untreated, or if it fails to respond to laxatives for more than a few days, water is progressively absorbed from the faecal mass in the sigmoid colon and rectum, and it becomes compressed and inspissated. This is faecal impaction, which may be relieved by the combined use of stimulant laxatives and enemas, but often needs manual evacuation.

Polyethylene glycol (PEG), in the molecular weight range 3200–4000, has been widely used for over 20 years as a non-absorbable osmotic agent in orally administered solutions for intestinal lavage preceding radiological and other diagnostic procedures. The addition of electrolytes produced 'balanced' solutions (PEG&E) that were designed to ensure negligible net absorption or elimination of sodium, potassium, bicarbonate and water while delivering a predictable non-absorbable osmotic load (Davis et al, 1980). Experience with PEG&E in intestinal lavage has shown a high success rate in the clearance of faeces, even in the presence of faecal impaction, with good tolerability and safety. Clearance of the bowel to give good results at barium enema or sigmoidoscopy requires 2–4 litres of PEG&E solution.

MOVICOL

Low-dose PEG&E (Movicol, Norgine, Harefield, Middlesex) for the treatment of all degrees of constipation was first launched in 1996 and was a logical development from the high-dose PEG&E products used for bowel lavage. This product contains 13.1 g of PEG 3350 per unit dose sachet together with 350.7 mg sodium chloride, 178.5 mg sodium bicarbonate and 46.6 mg potassium chloride. These quantities of electrolytes when made up in 125 ml of water provide 65 mmol/1 sodium, 53 mmol/1 chloride, 5.4 mmol/1 potassium and 17 mmol/1 bicarbonate. This concentration of electrolytes is calculated to facilitate their absorption at rates approximately equalling their rates of secretion, creating an overall net ion movement close to zero, irrespective of the dose given. The high-dose PEG&E products used for cleansing of the colon before surgery or diagnostic procedures deliver 200–400g of PEG3350 with appropriate amounts of electrolytes.

The osmotic pressure of the solution opposes absorption of water from the faecal material in the large bowel thus retaining water in the faeces, which causes the laxative action by both bulking and softening. This mode of action is in direct contrast to the osmotic laxatives which, by setting up a high osmotic pressure in the colon, cause water to be drawn in from the body. Thus low-dose PEG&E (Movicol) is best placed in a new class of laxatives, the 'iso-osmotic' laxatives.

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Movicol has two properties that justify its unique position as the only orally administered laxative that is effective for the treatment of faecal impaction as well as moderate to severe primary and secondary constipation:

Physiological inertness

PEG is physiologically inert, and is not absorbed from, or metabolized in, the gastrointestinal tract. This allows it to act osmotically to expand the faecal water over a large dose range, giving it an unlimited 'ceiling' of action. This is in contrast with other potent laxatives. Stimulant laxatives are subject to loss of sensitivity with long-term use, mineral laxatives are partially absorbed or exchange with other ions, and organic osmotic laxatives, such as lactulose, are metabolized by the colonic flora to absorbable metabolites and have a ceiling of action.

Prevention of dehydration

The end-effect of all laxatives, whether they act by pharmacological stimulation or by osmosis, is to increase the flow of faecal water. Severe constipation requires a large increase in flow to clear it, and this can induce dangerous dehydration and haemoconcentration in vulnerable patients.

More seriously, an obligatory loss of electrolytes accompanies any given volume of faecal water, and the loss is substantial with any laxative taken at high dosage or for prolonged periods.

The special property of Movicol here is that the content of water, sodium, potassium, bicarbonate and chloride are all set to give zero net transfer of electrolytes between the lumen of the gut and plasma. This is possible since PEG induces an increment in the flow of faecal water linearly related to the osmotic load that it delivers. This has been shown in human volunteers to hold for doses giving faecal water flows up to 1200 ml daily (Fordtran et al, 1990), in contrast to lactulose, which has a markedly non-linear dose–response relationship.

TABLE 1.
Comparison of PEG&E and placebo for assessment criteria

	Placebo	PEG&E	Change	*P*
Stools per week	4.7±4.55	9.36±4.35	4.66	<0.001
Difficulty	1.62±0.75	0.74±0.68	–0.87	<0.001
Satisfaction index	2.65±2.35	6.45±2.31	3.8	<0.001
Transit time (hours)	74±40.6	58.5±35.9	–16.6	<0.05
Enemas per subject	1.72±3	0.19±0.58	–1.53	<0.01

PEG&E = polyethylene glycol and electrolytes. From Lémann et al (1994)

MOVICOL IN CHRONIC CONSTIPATION

A placebo-controlled study and a comparative controlled clinical study with Movicol have been published.

Randomized, placebo-controlled trial

This study involved 39 patients, aged between 15 and 75 years, diagnosed as suffering from idiopathic chronic constipation. Patients with a stool frequency less than 3 per week for more than 3 months were included in a double-blind cross-over study, carried out in four centres (Lémann et al, 1994). During each treatment period of 15 days, patients received one sachet of Movicol (13.l g PEG) or a sachet of placebo (glucose and electrolytes, no PEG) in 125 ml water twice daily. If the response was insufficient by day 7, the dosage was increased to one sachet three times a day. There was a washout period of 3 days between the randomized treatments.

The main assessment criteria were number of stools, difficulty in passing stools (scale 0–3), and overall satisfaction index (scale 0–10). Other criteria were transit time, measured by radio-opaque marker, and frequency of enema usage. The results are shown in *Table 1*.

This study demonstrates the effectiveness of Movicol in improving bowel function and reducing intestinal transit time in chronically constipated patients over a 2-week period.

Randomized-controlled, comparative trial with lactulose

This trial was carried out in two consecutive parts. Part A was a randomized single blind parallel comparison of the effectiveness of PEG&E with lactulose, and part B was a subsequent open study of the effectiveness and safety of PEG&E over a 3-month period (Attar et al, 1999).

A total of 115 patients (21 male, 94 female), with a mean age of 55 years were recruited, and for part A were randomly allocated to Movicol or lactulose. All had suffered from constipation for at least 3 months, with fewer than three stools per week and/or with difficulty in evacuation. Of 60 patients allocated to Movicol, 23 had presented with infrequent and 6 with difficult defaecation while 31 had both symptoms. Of 55 patients allocated to lactulose, 26 had presented with infrequent and 8 with difficult defaecation, while 21 had both symptoms. The presenting symptoms were uniformly distributed in the Movicol and lactulose groups. Ten patients dropped out prematurely, leaving 52 on Movicol and 53 on lactulose for analysis.

In part A, patients took one sachet of Movicol (containing 13g PEG) or lactulose each morning

and evening for 30 days, except in cases of intolerance when the dose was reduced to one sachet daily. Patients recorded the frequency and difficulty of stool passage, their overall satisfaction with treatment and scores for gastrointestinal symptoms. The results are shown in *Table 2*.

Sixty five patients then entered part B for treatment with Movicol for 60 days on the same dosage basis as in part A. Of these patients, 39 had received Movicol and 26 had received lactulose in part A. Blood samples were taken on day 0 and day 60 for haematological and biochemical analysis. Six patients failed to complete part B, leaving 59 for analysis.

The mean frequency of stools remained more than 1 per day, and the difficulty of evacuation was consistently graded between 0–1 (normal to easy). There were no significant changes between day 0 and day 60 in electrolytes, haematological or renal function parameters. No serious adverse events related to treatment were recorded.

TABLE 2.
Comparison of the effectiveness of PEG&E *vs* lactulose

		Results (mean±SD)					
		Days 0–15			Days 0–30		
Parameter		PEG&E	Lactulose	*P*	PEG&E	Lactulose	*P*
No of stools/day		1.2±0.7	0.9±0.7	0.02	1.3±0.7	0.9±0.6	0.005
Difficulty in evacuation*		0.6±0.7	1.1±0.7	<0.001	0.5±0.6	1.0±0.7	<0.001
Overall satisfaction†		7.1±2.0	5.0±3.1	<0.001	7.4±2.5	5.2±3.3	<0.001
Symptom‡ score	Liquid stools	0.4±0.6	0.2±0.5	NS	0.3±0.5	0.2±0.5	NS
	Distension	0.8±0.8	1.0±1.0	NS	0.7±0.7	0.8±0.9	NS
	AP	0.5±0.7	0.7±0.9	NS	0.5±0.6	0.7±0.8	NS
	Rectal gas	0.8±0.6	1.0±0.9	NS	0.7±0.6	1.0±0.8	0.08
	Borborygmi	0 4±0 7	0 5±0 7	NS	0.3±0.5	0.5±0.6	NS

* 0 = easy, 3 = very difficult; † 0 = not satisfied, 10 = extremely satisfied; ‡ 0 = none, 3 = severe. AP = abdominal pain; NS = Not significant; PEG&E = polyethylene glycol and electrolytes; SD = standard deviation. From Attar et al (1999)

MOVICOL IN FAECAL IMPACTION

The results of two clinical studies have been reported.

Single treatment open study

Thirty patients, aged from 17 to 87 years, were recruited, and 27 completed the protocol, in a single treatment open study of Movicol in faecal impaction (Culbert et al, 1998). At entry all patients had a history of chronic constipation and of faecal impaction defined on the basis of five or more days without a bowel movement. Faecal loading was confirmed by physical examination of the abdomen and rectum.

Patients received the equivalent of 8 sachets of Movicol solution daily (1 litre) for 1, 2 or 3 days according to their response to treatment. This dose was set according to the results of a pilot study. Patients were assessed daily. The continuing presence of faecal impaction was assessed by physical examination of the abdomen and rectum, and bowel movements were evaluated by volume, number, form and ease of evacuation. Successful treatment was defined by a combination of the lack of palpable faecal loading and the report of a moderate or large stool. The overall results are shown in *Table 3*.

TABLE 3.
Response to PEG&E on each of 3 days of treatment

Number of doses	Patients completely cleared	At least 1 moderate or large stool
1	12/27 (44%)	16
2	23/27(85%)	25
3	24/27(89%)	27

PEG&E = polyethylene glycol and electrolytes. From Culbert et al (1998)

Of the 27 patients, 24 were regarded as 'completely cleared', and the other 3 as partially improved. All 27 patients passed moderate or large volumes of faeces after the last dose. All but two described evacuation as 'easy'.

Randomized trial of PEG&E *vs* lactulose and enemas

Forty five patients, aged from 70 to 91 years of age, with a prolonged history of constipation, and faecal impaction defined as the presence of hard faeces in the rectum, were randomly allocated to two groups. Both groups received daily enemas and lactulose twice daily; one group first received 2 litres of PEG&E on two consecutive days. Fifty six per cent were cleared of faeces within a week and 84% within 2 weeks, in contrast with 23% and 41% respectively of control patients (Puxty and Fox, 1986).

SAFETY AND ADVERSE EFFECTS

Open extensions of both the placebo-controlled and the comparative study took place for up to 2 months after the end of the randomized phase of the studies.

In the placebo-controlled study, 20 chronically constipated patients received Movicol, 2 or 3 sachets daily, for 3 months. There were no significant differences between days 0, 45 and 90 in terms of haemoglobin, leucocytes, platelets, plasma electrolytes, base reserve, urea, creatinine or transaminases.

In the comparative study out of the 99 patients who completed the randomized phase, 65 started on the open extension and 61 of these completed a further 2 months in the study.

The mean daily dose of Movicol over the 2-month period was 1.6 sachets. There were no significant changes in laboratory test result over the study with the exception of mean serum folate level; however, the individual values for each patient remained within the laboratory normal range at all time points.

PEG&E can cause symptoms attributable to the expansion of the intestinal tract, including distension, pain and nausea. Its contraindications are those common to all laxatives, namely intestinal perforation or obstruction, severe inflammatory conditions of the gastrointestinal tract and toxic megacolon. There is no published experience of the use of PEG&E during pregnancy or lactation. It is not recommended for use in children. It should be used with caution in patients with cardiac or renal impairment who are vulnerable to transient shifts in water and electrolytes.

DISCUSSION

Chronic constipation

Although the design of the multicentre study in 115 patients could have been improved by the addition of a baseline run-in period and a requirement for all patients to exhibit both infrequent defaecation and pain on evacuation, it nevertheless provides convincing evidence of the efficacy of Movicol.

It is possible to conclude that, at doses closely matched in terms of gastrointestinal symptom scores for liquid stools, abdominal pain and distension, rectal gas and borborygmi, Movicol shows significant superiority over lactulose in increasing stool frequency and relieving difficulty in evacuation. The beneficial effects of Movicol are sustained for a 90-day period, without serious adverse effects and without pathological changes in haematology and blood biochemistry.

Faecal impaction

The design of an objective study to evaluate an oral treatment for faecal impaction presents both ethical and operational problems. On the one hand it is hard to justify a blind placebo-controlled study in this condition; on the other, since there is no other oral treatment, comparison with invasive procedures with a high success rate but a finite risk would not be appropriate.

The open study recruited a small number of patients in the expectation of a high success rate. In fact total success was achieved in 24 out of 27 (89%) and partial clearance in the remaining three. In a condition where enemas and manual evacuations are the only alternative treatments, the study shows that Movicol is effective and safe, and highly acceptable to patients.

CONCLUSIONS

The oral therapy of moderate to severe constipation and of faecal impaction requires an agent that brings about a substantial increase in the flow of faecal water. Such an increase, whether brought about by osmosis or peristaltic stimulation, causes potentially severe haemoconcentration and electrolyte disturbances, particularly in vulnerable patients with cardiovascular and/or renal impairment. PEG is unique among such agents in having a predictable linear relationship between dose and faecal water content. This enables the required amount of water and electrolytes to be included in the product to achieve negligible net loss or gain of water and electrolytes. For this reason Movicol is the only oral agent licensed for the treatment of faecal impaction. HM

Conflict of interest: Dr A Ungar is a consultant to Norgine Ltd.

KEY POINTS

- Low dose polyethylene glycol with electrolytes (PEG&E) for treating constipation is a development of the iso-osmotic PEG&E products used for bowel preparation.
- PEG3350 is physiologically inert and is not absorbed from or metabolized in the gastrointestinal tract. It is combined with electrolytes to create Movicol, a PEG&E preparation.
- One sachet of Movicol is dissolved in 125 ml of water to produce an iso-osmotic solution and, depending on the age of the patient, 1–3 sachets a day is effective in treating constipation.
- Eight sachets of PEG&E dosed in 1 litre of water daily is effective in clearing faecal impaction in 85% of patients after 2 doses.
- Movicol is the only orally administered product that is licensed for faecal impaction.

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