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Acceptability Flavour Test of Polyethylene Glycol-Based Laxative Bimotil® in Comparison with Movicol®

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ABSTRACT

Background: Polyethylene glycol (PEG) is an osmotic laxative considered as pharmacological first line choice for the treatment of chronic functional constipation and fecal impaction. Addition of electrolytes to PEG is a relevant clinical advantage since can minimize plasma electrolyte loss, improve safety, and even enhance the laxative effect. Bimotil® with PEG-3350 and electrolytes (PEG-ELS) is a newly developed medicinal product with 2 different strengths: 13.7 g for adolescents, adults, and the elderly; and 6.9 g for children. Since the palatability of PEG-based laxatives with electrolytes is challenging, and relevant to improve acceptability and adherence (warranting therapeutic compliance) an acceptability comparative study versus Movicol® at adult and pediatric strengths has been conducted.

Methods: At strengths for adolescents, adults and the elderly, an ad hoc questionnaire with 3 sub-questionnaires (demographics, organoleptic and comparative preference) was designed. Organoleptic sub-questionnaire assessed acceptability and rates of taste attributes of sweet, salty and intensity flavor; and comparative sub-questionnaire included key forced overall preference, increasing willingness to take the product, and preference for repeated use items. At strengths for children, comparative key forced overall, and repeated use preference were assessed. Medicinal products were blindly presented to properly instructed subjects. The low amount of administered product made the occurrence of adverse effects very unlikely; anyway, a safety certificate was prepared.

Results: In the adult sub-study (n=80), Bimotil® 13.7 g and Movicol® 13.8 g were compared with relevant statistically significant differences favoring Bimotil® 13.7 g in key forced overall preference (76.3% vs. 23.8%, $p < 0.05$), acceptability rate (1-9) (5.75 vs. 4.84, $p < 0.05$), willingness to multi-taking the product rate (1-9) (6.35 vs. 4.75, $p < 0.05$), and preference for repeated use (76.3% vs. 23.8%, $p < 0.05$). Moreover, Movicol® 13.8 g was negatively valued in the 3-taste attributes. In the children sub-study (n=60), Bimotil® Infantil 6.9 g was significantly better than Movicol® Pediatrico Sabor Neutro 6.9 g in forced overall preference (65.0% vs. 35.0%, $p < 0.05$) and preference for repeated use (68.3% vs. 31.7%, $p < 0.05$).

Conclusions: Bimotil® has shown relevant advantages in palatability and acceptability in adults and children, in comparison with Movicol® 13.8 g and Movicol® Pediatrico Sabor Neutro, respectively.

Keywords: Acceptability; Constipation; Electrolytes; Laxatives; Palatability; Polyethylene Glycol

Introduction

Chronic constipation is one of the most common gastrointestinal disorders worldwide in adults and children and, in the more severely affected individuals with fecal impaction, has been associated to significant impairments in quality of life and social functioning [1]. In the adult population, chronic constipation is a very common condition. Prevalence has been world-wide estimated around 15-17% [1] and increases with the age, especially in those over 65 years and in women, being around three times more common in the latest [2]. Chronic constipation may affect more than 70% of people living in nursing homes. The high prevalence of constipation in institutionalized elderly patients results in reduced quality of life and high economic burden, and it is also associated with the potentially serious complications of fecal impaction [3]. In the pediatric population, prevalence reports considerably vary from 1% to 30%

(median 10.4%), according to literature [1]. These wide variations could be probably explained because there is no general agreement on constipation definition in children [4].

Constipation can be classified into two types: primary and secondary constipation. Primary constipation is related to disorders in the regulation of the neuromuscular components of the colon and anorectum, as well as disruption in their corresponding ascending and descending neural pathways in the brain-gut axis. Primary constipation can be further classified into functional defecation disorder, slow-transit constipation, and constipation-predominant irritable bowel syndrome. Secondary constipation can result from many factors such as metabolic disturbances; medications such as opiates, calcium channel blockers, antipsychotics; neurologic disorders (e.g. parkinsonism, spinal cord lesions, diabetes mellitus), or diseases of the colon (cancer, anal, fissure or proctitis, among others) [5]. Specifically in children, constipation is generally functional, with no objective evidence of an identifiable pathological condition. In fact, most of the time the cause of constipation in children is the development of stool withholding behaviour after a painful frightening evacuation experience [6].

The initial management of chronic constipation in children or adult population includes behaviour modification and/or dietary changes. For patients who do not respond to this management, laxatives should be considered as pharmacological treatment and, according to guidelines, the use of osmotic laxatives such as PEG-based medicinal products, with or without electrolytes, is considered as first choice for the pharmacological treatment of functional constipation when medically indicated [7]. A systematic review and meta-analysis found that PEG plus electrolytes (PEG-ELS), among other laxatives, is more effective than placebo in treating chronic constipation in adults [8]. Specifically, in some RCT, PEG-ELS has shown advantages in efficacy and/or safety, in comparison with other laxatives such as lactulose [9] or tegaserod [10]. Moreover, in pediatric patients aged 0 to 18 years old, a systematic review of randomized controlled trials (RCT) which compared osmotic or stimulant laxatives with placebo, or another intervention was conducted. The pooled analyses of 25 RCTs (which included 2,310 patients) suggested that PEG preparations may be superior to placebo or other therapeutic approaches such as lactulose and milk of magnesia for the treatment childhood constipation [11].

Addition of electrolytes to PEG is widely considered a relevant clinical advantage because their iso-osmotic composition can minimize the plasma electrolyte loss across the gastrointestinal lumen. The water retention of PEG without electrolytes -its essential laxative mechanism of action- causes electrolyte loss to compensate the osmotic imbalance in the gastrointestinal lumen which remains hypo-osmotic because of the absence of electrolytes, as well as the fact that commonly added electrolytes in PEG medicinal products such as sodium can contribute to the laxative effect of the mixture [12,13]. It is known that one of the potentially most relevant medical complications of misuse of laxatives are electrolyte disturbances, mainly electrolyte loss, which can be of special clinical relevance in eventual vulnerable patients at risk of dehydration such as children, elderly, and also in patients with heart or kidney diseases, among other conditions. In this sense, hypokalaemia has been related to muscle weakness and lassitude, as well as renal and cardiovascular disorders. Other electrolyte disturbances caused by excessive laxative activity may lead to dehydration, hypotension, tachycardia, postural dizziness, and syncope [14]. Therefore, and probably due to the reasons mentioned above, the most used PEG-based laxatives by far are the ones which include electrolytes (PEG-ELS). In fact, medicinal products with PEG without electrolytes are not considered iso-osmotic and, therefore, are not authorized for its clinical use in fecal impaction [15]. It has been shown in children with chronic constipation that PEG without electrolytes caused more electrolytes disturbances than PEG-ELS [16]. Furthermore, some comparative studies between PEG without electrolytes and PEG-ELS have found some slight advantages in terms of stool consistency in favour of PEG-ELS [13].

PEG-ELS formulations are often characterized by an unpleasant taste due to the presence of salts as source of the electrolytes in the formulation; but, otherwise, patient´s acceptability of oral medicinal products is a relevant matter in relation with the effectiveness of laxative treatment, mainly in the long-term, and it could be a challenge concerning medicinal products with PEG and electrolytes since its eventual lack of palatability might imply a reduced acceptability and, hence, compromise adherence to laxative treatment [6]. Consequently, there are strong arguments to claim that a good acceptability of PEG-ELS product which are widely recommended for the treatment of chronic constipation and fecal impaction [7] can positively influence on improving laxative adherence and, hence, compliance and success of treatment. In this sense, ITF Research Pharma, S.L.U. (Spain) has designed and developed Bimotil®, a new laxative medicinal product based on PEG-3350 plus electrolytes with a mixed citric mainly orange/ slightly lemon flavour to overcome the barrier of the taste and, therefore, to maximize acceptability, both for adults and children. Bimotil® has been developed with 2 different strengths: one with a dosage 13.7 g indicated for adolescents, adults, and the elderly; and another one with 6.9 g for children [17].

To ascertain the good palatability, and thus, acceptability of Bimotil®, we performed a comparative study comparing Bimotil® 13.7 g sachet, powder for oral solution (Bimotil® 13.7 g) with Movicol® 13.8 g sachet, powder for oral solution (Movicol® 13.8 g) as market leader of laxative macrogol-based medicinal products in adults [17]; and another one comparing Bimotil® 6.9 g sachet, powder for oral solution (Bimotil® Infantil) with Movicol® Pediatrico Sabor Neutro 6.9 g sachet, powder for oral solution (Movicol® Pediatrico Sabor Neutro), as market leader of laxative macrogol-based medicinal products in children [18]. The aim of our research was to assess relevant differences between the 2 medicinal products in terms of organoleptic evaluation (taste acceptability) and individual preference (preference of taste, willingness to consume the product and preference of taste to consume the product repeatedly).

Materials and Methods

Test Products

We compared acceptability of Bimotil® 13.7 g versus Movicol® 13.8 g for adolescents, adults, and the elderly (adult sub-study); and Bimotil® Infantil versus Movicol® Pediatrico Sabor Neutro for children from 8 to 12 years old (children sub-study). We decided to compare our products with the leading market laxative macrogol-based medicinal products (Movicol® 13.8 g for adolescents, adults, and the elderly; and Movicol® Pediatrico Sabor Neutro for children) [18], as we ascertained that these macrogol-based laxative presentations were the most accepted ones by prescribers and patients and, therefore, could provide our research with more objectivity and less selection bias.

Population of the Study

A sample size of 80 subjects (50% male, 50% female; 12 to 65 years old; proportionally balanced for 12-17, 18-34, 35-54, and 55-65 age groups) in the adult sub-study; and a sample size of 60 subjects (50% male, 50% female; 8 to 11 years old) in the children sub-study; were both estimated for detecting statistically significant acceptability differences between the 2 medicinal products at the 2 different strengths.

Methodology

The study was conducted in Silliker center, provided with their own tasting room according to UNE-EN ISO 8589:2010 quality certificate. The two medicinal products were blindly presented to every individual in 20 ml amounts served in white glasses with neutral and biodegradable organoleptic characteristics. The taste temperature was 24 ºC + 2 ºC.

Comparative Sub-Study in Adults: we designed a questionnaire composed by 3 sub-questionnaires covering demographics (sex and age), organoleptic and comparative preference items, respectively.

The organoleptic preference sub-questionnaire contained:

A) A key acceptability flavour question rated from 1 ("dislike very much") to 9 ("like very much") to assess the overall acceptability of the taste of each product as evaluated individually.

B) Taste attribute questions rated from 1 ("too little") to 5 ("too much") concerning intensity of sweet flavour, intensity of salty flavour and overall intensity, respectively. These 3 questions were JAR (just about right) scales in which the JAR rate was categorized as optimal acceptance and corresponded to the 3-value. This test investigates how the products are perceived in terms of sweetness, saltness and overall.

The comparative preference sub-questionnaire had 3 items to directly ask which one of the two products were preferred as single intake (key forced overall preference) and also in terms of repeated intake and additionally envisioning a 1-3 daily dose for 3 weeks.

A) Key forced overall preference.

B) Increasing willingness to take the medicinal product (supposing 1 to 3 daily doses for 3 weeks) rated from 1 ("very unwilling") to 9 ("very willing").

C) Forced flavour preference (supposing 1-3 daily dose for 3 weeks).

Comparative Sub-Study in Children: we designed a pediatric comparative preference sub-questionnaire including 2 items:

A) Key forced overall preference.

B) Repeated use preference.

Every individual (adolescent, adult, or elderly; or children from 8 to 12) answered the questionnaires after taking Bimotil® 13.7 g / Bimotil® Infantil or Movicol® 13.8 g / Movicol® Pediatrico Sabor Neutro, being instructed to take enough water to cleanse the palate and wait at least a minute until taking the other medicinal product.

Safety

A safety certificate was prepared and signed, considering the improbability for potential adverse events (mainly gastrointestinal such as abdominal pain, borborygmi, diarrhea, vomiting, nausea, or anorectal discomfort) due to the minimum intake of the medicinal products. Anyway, the study was performed in healthy subjects and individuals were not included if medicinal products could be contraindicated (patients with intestinal perforation or obstruction due to structural or functional disorder of the gut wall; ileus; or severe inflammatory conditions of the intestinal tract such as Crohn's disease ulcerative colitis or toxic megacolon) [17].

Statistical Analysis

Statistics were performed to detect if differences (mean or %) were significantly different at a 95% confidence interval. For flavour acceptability and willingness to take the medicinal products we used a complete block analysis of variance (ANOVA) and Tukey test; but for rates 8+9, we used chi square test and Marascuilo procedure. For JAR questions we used penalty analysis and Tukey test; and for forced flavour preference, we used a paired comparison test. We performed descriptive statistics and graphs.

Results

Demographics

Demographic main characteristics of included subjects are shown in Figure 1. 80 subjects were finally included in adult sub-study (> 12 years old); and 60 in children sub-study (8-12 years old).

Organoleptic Preference

In the adult sub-study, there was a statistically significant difference between Bimotil® 13.7 g and Movicol® 13.8 g acceptability rate (1-9): 5.75 vs. 4.84, $p < 0.05$ (see Figure 2). Also in adults, Bimotil® 13.7 g was considered as JAR (just about right) for most of subjects while Movicol® 13.8 g was negatively valued in the three taste attributes (sweet flavor intensity, salty flavor intensity, and

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overall intensity). Moreover, all the JAR % were numerically higher for Bimotil® 13.7 g. See Table 1 with non-JAR taste attributes in red as for % of unsatisfied (too much or too little; sweet, salty, or overall) individuals higher than 30%.

Figure 1a Figure 1b

Age (%)	
12-17 years old	23.8%
18-34 years old	20.0%
35-54 years old	28.8%
55-65 years old	27.5%

Figure 1: Demographic characteristics of subjects in

a. Adult sub-study; and

b. Children sub-study.

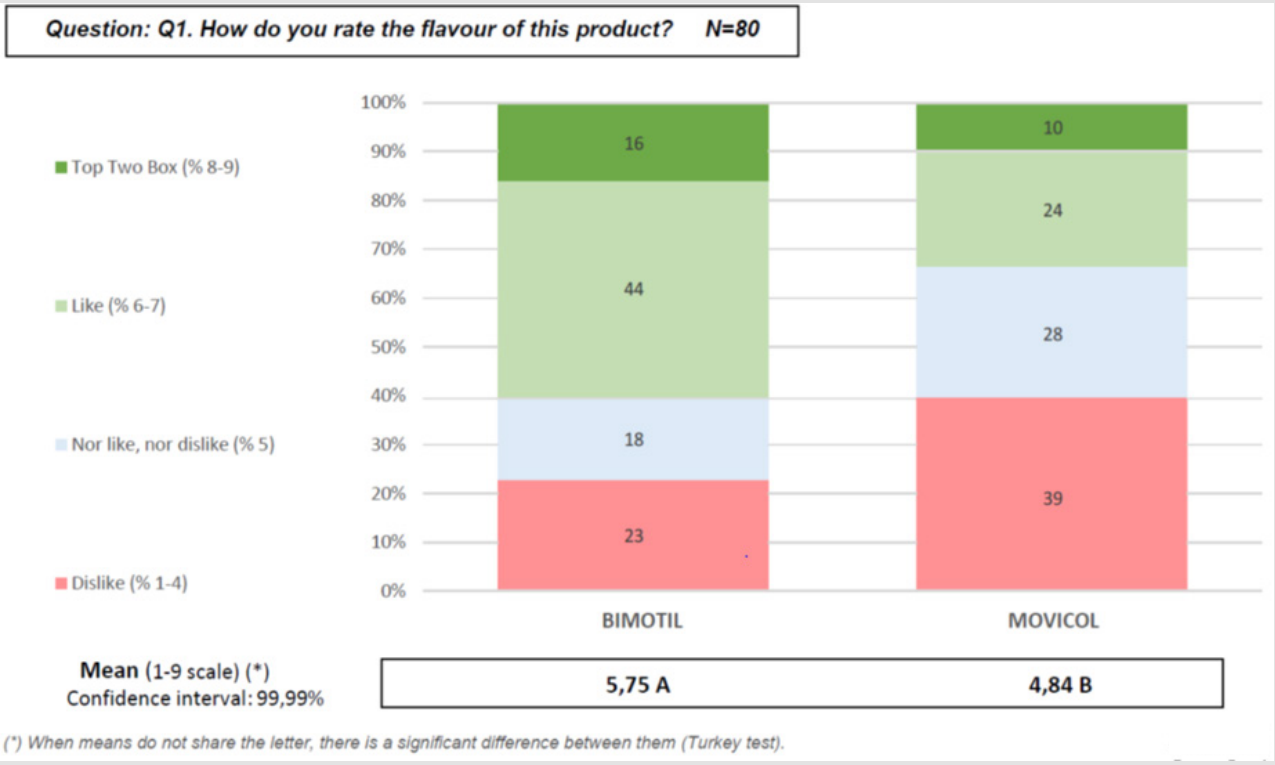

Figure 2: Key acceptability question in adult sub-study.

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Table 1: Taste attributes in adult sub-study.

			BIMOTIL	MOVICOL
Sweet flavour intensity	Too much sweet	(%)	18%	5%
	Just about right	(%)	48%	25%
	Too little sweet	(%)	35%	70%
Salty flavour intensity	Too much salty	(%)	23%	38%
	Just about right	(%)	59%	43%
	Too little salty	(%)	19%	20%
Overall intensity	Too much intense	(%)	26%	19%
	Just about right	(%)	48%	33%
	Too little intense	(%)	26%	49%

Comparative Preference

In adults, Bimotil® 13.7 g and was significantly preferred in comparison with Movicol® 13.8 g (76.3% vs. 23.8%, $p < 0.05$) (see Figure 3a). Concerning willingness to proposed repeated use (1-3 daily dose for 3 weeks), there was also a statistically significant difference between Bimotil® 13.7 g and Movicol® 13.8 g in terms of 1-9 rate (1 - "very unwilling" to 9 - "very willing") in adults (6.35 vs. 4.75, $p < 0.05$). Superiority of Bimotil® 13.7 g was also observed in forced preference for repeated use in adults (76.3% vs. 23.8%, $p < 0.05$). Similarly to the adult population, children also preferred Bimotil® Infantil over Movicol® Pediatrico Sabor Neutro, on the 2 items included in the pediatric comparative preference sub-questionnaire: key forced overall preference (65.0% vs. 35.0%, $p < 0.05$) (see Figure 3b) and repeated use preference (68.3% vs. 31.7%, $p < 0.05$).

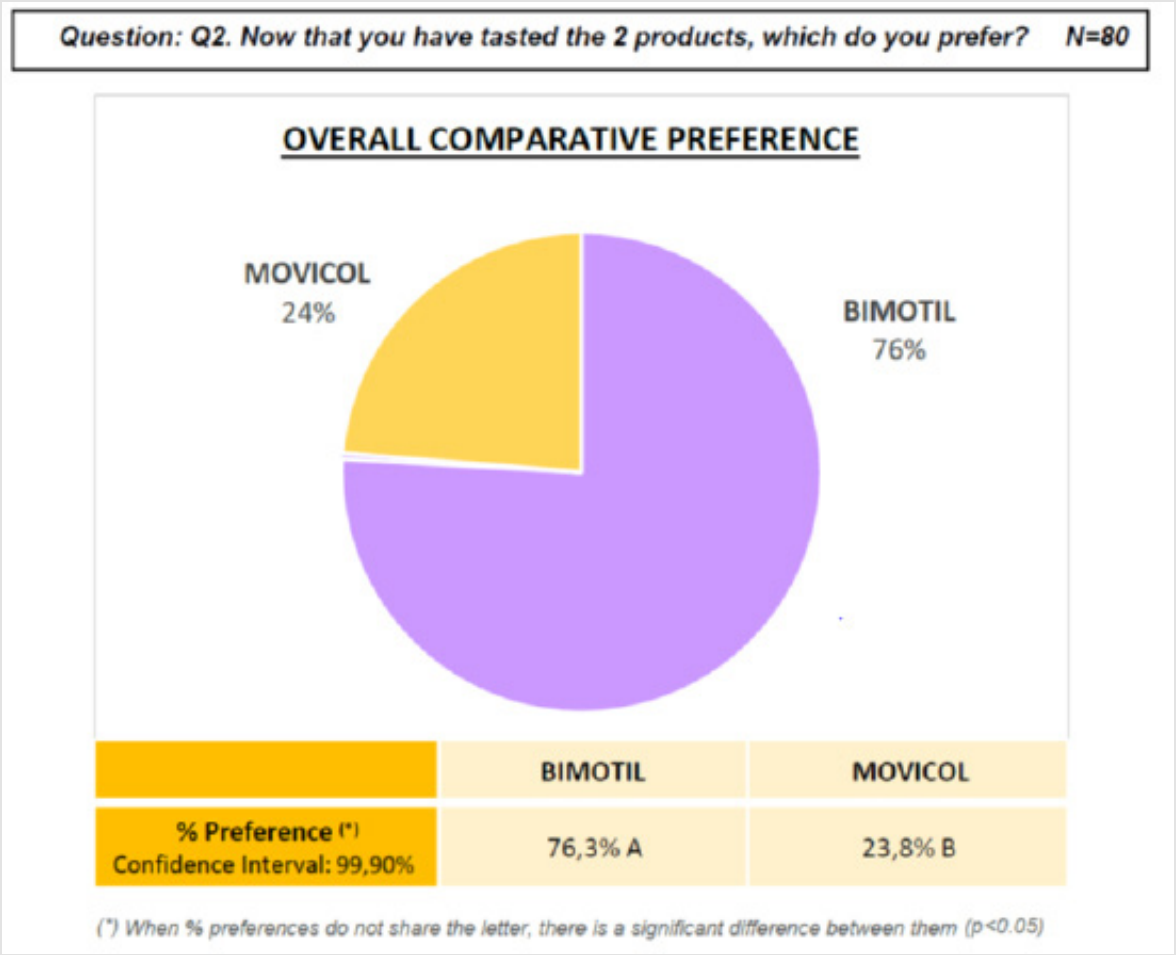

Figure 3a: Overall comparative preference in Adult sub-study

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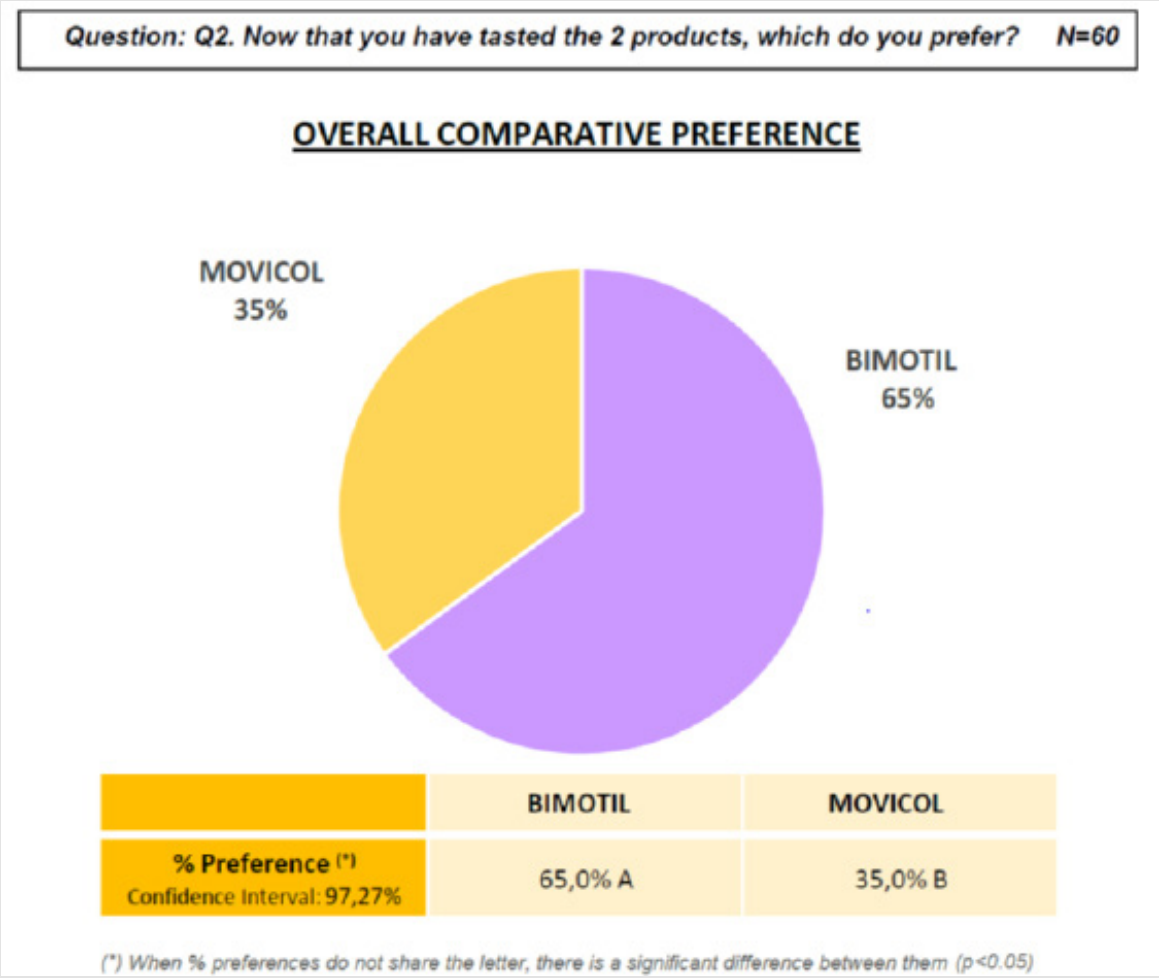

Figure 3b: Overall comparative preference in Children sub-study.

Discussion

As previously mentioned, PEG-ELS medicinal products are indicated as first line for the pharmacological treatment of chronic constipation and fecal impaction [7,15], being the addition of electrolytes clinically relevant in order to avoid the potential electrolyte loss which could be related to long-term laxative treatment [13] and their negative clinical implications [14]. Anyway, and since the presence of electrolytes represents a challenging issue in terms of flavor acceptance of laxative medicinal products, we have developed Bimotil® as a PEG-ELS medicinal product focused in optimizing the palatability and, eventually, improving the flavor and taste of other similar laxative medicinal products leading the laxative market in our healthcare system. In this sense, Bimotil® has been formulated with a specific composition of excipients which provide the medicinal product with a pleasant citric flavor (mainly orange and slightly lemon) intended to mask the electrolyte content.

According to our findings, when assessing acceptability, taste attributes, preference, and willingness repeated use, there were significant differences in favour of Bimotil® 13.8 g in comparison with Movicol® 13.8 g in adults. In children, we found significant superiority of Bimotil® Infantil in terms of overall preference and forced preference for repeated use, confirming that masking the taste of electrolytes is crucial for acceptability of the product, as we compared with a neutral flavour in children. Our research has some limitations, being the main of them that the study was single but not double-blinded. Anyway, the instructions to the individuals, as well as the presentation of the two products were identical to minimize selection bias as much as possible.

Conclusion

Addition of electrolytes to PEG is widely recognized as a relevant clinical advantage because it can prevent the electrolyte loss and its eventual associated adverse events; but the flavor acceptability of PEG-ELS laxative medicinal products may be a challenging issue. Bimotil®, our new PEG-3350 with electrolytes laxative medicinal product, has proven to have relevant advantages in palatability and flavor acceptability in children and, especially, in adults, in comparison with the reference product Movicol® 13.8 g / Movicol® Pediatrico Sabor Neutro. This acceptability improvement of Bimotil®

could be translated into a better treatment adherence, which might be of great relevance considering laxative treatment is often long-term.

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