

# The safety of osmotically acting cathartics in colonic cleansing

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**Abstract** | Efficient cleansing of the colon before a colonoscopy or a radiological examination is essential. The osmotically acting cathartics (those given the Anatomical Therapeutic Chemical code A06AD) currently used for this purpose comprise products based on three main substances: sodium phosphate, combinations of polyethylene glycol and electrolyte lavage solutions (PEG–ELS), and magnesium citrate. All these preparations give adequate cleansing results and have similar profiles in terms of the frequency and type of mild to moderate adverse effects. However, serious adverse events, such as severe hyperphosphatemia and irreversible kidney damage owing to acute phosphate nephropathy, have been reported after use of sodium-phosphate-based products. The aim of this Review is to provide an update on the potential safety issues related to the use of osmotically acting cathartics, especially disturbances of renal function and water and electrolyte balance. The available evidence indicates that PEG–ELS-based products are the safest option. Magnesium-citrate-based, hypertonic products should be administered with caution to elderly individuals and patients who are prone to develop disturbances in water and electrolyte balance. Sodium-phosphate-based products can occasionally cause irreversible kidney damage and should not be routinely used in bowel-cleansing procedures.

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## Introduction

Efficient cleansing of the colon before an endoscopic or radiological examination is an essential prerequisite for optimal evaluation.<sup>1,2</sup> Three main types of osmotically acting cathartics (which are assigned the WHO Anatomical Therapeutic Chemical [ATC] code A06AD<sup>3</sup>) are currently used as bowel-cleansing agents: sodium-phosphate-based products, polyethylene glycol and electrolyte lavage solutions (PEG–ELS), and magnesium-citrate-based products. These groups of cathartics are all effective and have similar safety profiles in terms of their mild to moderate adverse effects, such as bloating, vomiting, and gastrointestinal discomfort,<sup>4,5</sup> which are experienced in approximately 50% of all patients.<sup>6–8</sup>

Both sodium-phosphate-based and magnesium-citrate-based products are hypertonic, and their principle mode of action is to extract and then retain fluid by osmosis into the intestinal lumen, which induces diarrhea that empties the colon.<sup>5</sup> Owing to the hypertonic characteristics of these solutions, they have the potential to cause substantial disturbances in fluid and electrolyte balance by inducing net transport of ions across the intestinal mucosa.<sup>5</sup> Passive absorption of the supraphysiological amounts of phosphorus and magnesium contained in these products often leads to some degree of hyperphosphatemia and hypermagnesemia, respectively.

Isotonic PEG–ELS products consist of a polyethylene glycol (PEG) polymer with electrolyte solutions added to

produce a fluid that is iso-osmotic with plasma.<sup>5</sup> These products, in contrast to the hypertonic solutions, do not generally cause marked shifts in water, mineral or electrolyte balance because they are minimally absorbed and do not cause a net excretion or absorption of ions across the intestinal mucosa.<sup>5,9,10</sup> Their main mode of action is evacuation of the bowel by high-volume lavage, accomplished through ingestion of nonabsorbable fluid.<sup>5</sup> For the purposes of this Review, PEG–ELS products are nonetheless included within the group of osmotically acting cathartics because their main constituent is macrogol, which has been assigned an ATC code of A06AD.

Bowel-cleansing procedures, regardless of which agent and regimen is used, can result in dehydration and changes in serum levels of electrolytes (sodium in particular) owing to their effects on the gastrointestinal system—both wanted (for example, diarrhea) and unwanted (for example, vomiting). Sufficient hydration of patients undergoing these procedures is, therefore, essential.<sup>11</sup> A number of safety issues are associated with colon-cleansing procedures (Figure 1), namely, the risk of missed pathological lesions owing to inadequate cleansing, rare procedural adverse events such as Mallory–Weiss tears and esophageal rupture, and the risk of aspiration during nasogastric tube administration of agents to patients who are unable to ingest the solution orally (Box 1).<sup>12–20</sup> This Review discusses the safety and adverse effects of the most commonly used osmotically acting cathartics. The article focuses on the negative effects of these agents on kidney function as well as

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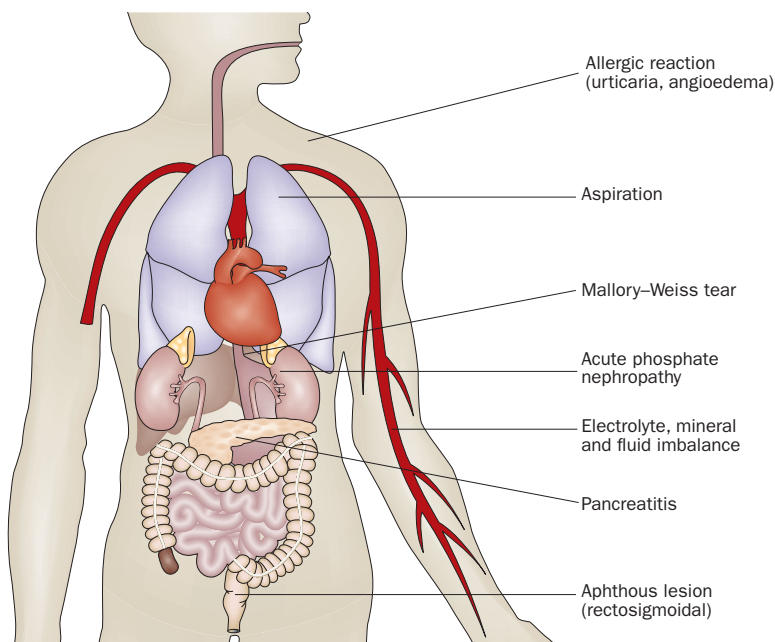
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## Competing interests

The authors declare no competing interests.

**Key points**

- Bowel-cleansing procedures can have dehydrating effects; ensuring sufficient hydration of patients is, therefore, essential
- In patients with relevant comorbidities or those on medications that influence water and electrolyte balance, iso-osmotic preparations are safer options than hyperosmotic products
- Monitoring of serum electrolytes is recommended in patients treated with osmotically acting cathartics (especially individuals with relevant comorbidities and those on medications that influence the water and electrolyte balance)
- Routine use of sodium-phosphate-based cathartics is not recommended because of their potential serious adverse effects on kidney function



**Figure 1** | Adverse events associated with use of the three major types of osmotically acting cathartics. The three main groups of osmotically acting cathartics used for bowel cleansing are polyethylene glycol (in combination with electrolyte lavage solution), sodium-phosphate-based agents and magnesium-citrate-based products. Use of these cathartics can be associated with adverse events such as electrolyte, mineral and fluid imbalances, allergic reactions (urticaria and angioedema), aspiration, Mallory–Weiss tears, pancreatitis, aphthous lesions (rectosigmoidal) and the serious adverse event of acute phosphate nephropathy (and, possibly, irreversible kidney damage).

disturbances in the water and electrolyte balance and concludes with recommendations to optimize the selection of agents for bowel cleansing.

**Sodium-phosphate-based products**

Sodium-phosphate-based cathartics are typically administered as two separate doses of aqueous solutions of 30–45 ml (each 45 ml dose containing 29.7 g sodium phosphate), given 10–12 h apart.<sup>5</sup>

**Serious adverse effects**

In several patients the use of sodium-phosphate-based bowel-cleansing products has led to severe disturbances in fluid, mineral and electrolyte balance. Reports have shown marked changes in serum levels of phosphorus (that is, hyperphosphatemia), calcium (that is, hypocalcemia),

**Box 1** | Adverse effects of osmotically acting cathartics\*

- Sodium phosphate
- Hyponatremia
  - Hypernatremia
  - Hyperphosphatemia, hypokalemia and hypocalcemia
  - Acute phosphate nephropathy
  - Aphthous ulcers (rectosigmoidal)
- Magnesium citrate
- Hyponatremia
  - Hypermagnesemia
  - Dehydration
- Polyethylene glycol lavage
- Hyponatremia
  - Hypernatremia
  - Hypokalemia and hypomagnesemia
  - Aspiration
  - Allergic reactions
  - Mallory–Weiss tears
  - Pancreatitis

\*Including occasional events presented as single cases.

and potassium (that is, hypokalemia) in up to 87%, 58%, and 56% of users, respectively, after intake of sodium-phosphate-based cathartics.<sup>21–23</sup> The highest incidence of hypokalemia and hypocalcemia was found in a study by Beloosesky and colleagues.<sup>22</sup> These researchers investigated electrolyte disorders in elderly patients (≥65 years) and found that this age group might have an increased susceptibility for developing such disturbances after bowel cleansing with sodium-phosphate-based products.<sup>22</sup> The shifts in fluid, mineral and electrolyte balance are usually reversible and asymptomatic, but several serious adverse events of clinical importance can occur, including hyperphosphatemia (with hypocalcemia) and rare events of hypernatremia and hyponatremia.<sup>24–43</sup> The majority of reported cases of severe hyperphosphatemia have occurred as a result of inappropriate use, that is, in patients with contraindications to administration of sodium-phosphate-based cathartics (such as renal failure<sup>29,36,43</sup> and colonic ileus<sup>30</sup>) and/or excessive dosing.<sup>25,26,31,38,40,41</sup> Studies that investigated the physiological effects of sodium-phosphate-based cathartics have reported a substantial decrease in body weight and an increase in plasma osmolality and tongue dryness (in patients ≥80 years of age), which indicates that these cathartics have dehydrating effects.<sup>44,45</sup> Furthermore, sodium-phosphate-based products can cause rectosigmoid aphthous lesions (similar to those in patients with IBD), which potentially causes a diagnostic problem and can confuse the diagnosis of other intestinal disorders using colonoscopy.<sup>46–48</sup>

In addition to the above-mentioned electrolyte and mineral disturbances, several reports of acute phosphate nephropathy (APN) in patients undergoing bowel-cleansing procedures have been published.<sup>49–60</sup>

The incidence of APN related to sodium-phosphate-based cathartics is unknown, but experts estimate that it occurs in less than one in 1,000 individuals.<sup>61</sup> The exact pathophysiological mechanism that underlies APN has not yet been fully clarified. However, the supra-physiological amounts of phosphorus provided (up to 59.4 g sodium phosphate, equivalent to 11.52 g of elemental phosphorus<sup>62</sup>), possibly in combination with a reduction in plasma volume, are thought to result in a changed calcium-phosphorus solubility product that can lead to precipitation of calcium phosphate crystals in the renal tubuli and subsequently to chronically impaired kidney function.<sup>56</sup> Hyperphosphatemia has been observed to cause an increase in parathyroid hormone secretion (that blocks phosphate reabsorption in the renal tubuli) and a decrease in total, as well as ionized, serum calcium levels.<sup>63</sup> A low body weight (with consequently low total water and lean body mass) seems to predispose patients to hyperphosphatemia; low-body-weight individuals ( $\leq 55$  kg) can develop higher serum phosphate levels for a longer period of time compared with heavier individuals ( $>100$  kg) after ingestion of similar doses of sodium phosphate.<sup>62</sup> These effects occur even with sufficient hydration, but worsen if patients develop nausea and vomiting or do not have an adequate fluid intake.<sup>62</sup> Although APN is rare, the severity of this adverse event led to the withdrawal of sodium-phosphate-based products from over-the-counter sales (for purgative use) in the USA and Canada, and revised recommendations for use of these agents have been issued.<sup>64,65</sup>

### Risk factors for adverse events

Comorbidities or medications that affect the glomerular filtration rate (by decreasing renal elimination of phosphorus), intestinal function (by increasing uptake of phosphorus), and water and electrolyte balance are thought to aggravate hyperphosphatemia, thereby predisposing patients with these risk factors who are treated with sodium-phosphate-based cathartics to the development of APN (Box 2).<sup>51</sup> Findings from retrospective studies have shown that advanced age,<sup>66</sup> congestive heart failure,<sup>66</sup> chronic kidney disease,<sup>67-69</sup> diabetes mellitus,<sup>67</sup> and the use of medications such as angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers<sup>67</sup> and NSAIDs are important factors in the development of impaired kidney function after the use of sodium-phosphate-based cathartics.<sup>69</sup> Additionally, advanced age and elevated pretreatment serum levels of creatinine show a positive correlation with increased serum phosphate concentrations after use of these agents.<sup>21,62,70</sup> Hypertension and female sex are other important risk factors found in the majority of cases of biopsy-proven APN.<sup>71</sup> The effects of administration of sodium-phosphate-based products to individuals with previously normal kidney function have been investigated in retrospective studies, but a clear association between this group of cathartics and renal damage has not been consistently demonstrated. Some investigators have suggested that no such association exists,<sup>72-75</sup> whereas others have concluded that the use of sodium phosphate cathartics, even in recommended

### Box 2 | Risk factors for acute phosphate nephropathy

- Female sex
- Age 60 years or older
- Chronic kidney disease
- Hypertension
- Treatment with angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, diuretics and/or NSAIDs
- Congestive heart failure
- Diabetes mellitus
- Low body weight

dosages, can lead to notable renal impairment.<sup>66,67,69</sup> Some of the most alarming observations are from a study by Khurana and colleagues,<sup>67</sup> in which the glomerular filtration rate irreversibly declined from 79 ml/min/1.73 m<sup>2</sup> to 73 ml/min/1.73 m<sup>2</sup> at 6 months after a single exposure to a sodium phosphate preparation in otherwise healthy elderly persons (average age 68 years).<sup>67</sup> Results from a retrospective study that investigated the renal effects of sodium-phosphate-based cathartics in patients with pre-existing renal impairment showed that an already decreased kidney function is further impaired after the use of sodium-phosphate-based products in colon-cleansing procedures.<sup>68</sup> Only one small prospective study has specifically investigated the renal effects of sodium phosphate; this study found no marked renal impairment related to the use of sodium-phosphate-based cathartics.<sup>76</sup> When interpreting the results from these studies, however, it should be noted that no general consensus definition of 'markedly affected renal function' exists.

### Polyethylene glycol lavage

PEG is absorbed to a minimal extent in the intestine, even if the gut mucosa is not intact (for example, in patients with IBD).<sup>9,10</sup> PEG is considered an osmotically acting substance, although the PEG-based products used for colon cleansing also contain added electrolytes, to create an iso-osmotic solution. Owing to their isotonic nature, PEG-ELS solutions must be consumed in a substantially larger amount of fluid (2–4 l, depending on the regimen applied) than hypertonic preparations. The 4 l volume of the standard preparation has caused problems with compliance, as some patients—up to 38% in some studies—have trouble ingesting the whole amount of fluid.<sup>27,77-79</sup> To ameliorate this problem, split-dose regimens and reduced-volume options (in combination with additional agents such as magnesium citrate, bisacodyl or ascorbic acid) have been developed to reduce the patient's discomfort.<sup>80-89</sup>

Reports of electrolyte disturbances related to intake of PEG-ELS solutions have consisted of occasional cases of dysnatremia (hyponatremia and hypernatremia)<sup>90-92</sup> as well as one case of hypokalemia and hypomagnesemia.<sup>93</sup> Dysnatremia is believed to occur as a result of salt loss caused by diarrhea, vomiting, and inadequate or excessive water intake during the cleansing procedure. Elderly patients with reduced thirst and/or diminished renal handling of water are especially prone to develop

electrolyte disturbances.<sup>94,95</sup> Some reports suggest that an altered level of antidiuretic hormone (ADH) is pivotal for the development of hyponatremia. This theory is supported by a small study by Cohen and colleagues,<sup>96</sup> who found substantial changes in ADH in patients with low serum levels of sodium after a gut lavage procedure.<sup>96</sup> Changes in ADH levels in the syndrome of inappropriate ADH release can be provoked by stimuli such as nausea, anxiety, treatment with selective serotonin reuptake inhibitors and advanced age.<sup>91</sup>

A retrospective chart review by Ho and colleagues<sup>97</sup> found a 9.6% incidence of hypokalemia ( $\leq 3.0$  mmol/l) in elderly hospitalized patients ( $\geq 65$  years of age) with relevant comorbidities (in particular, cardiac and renal disease). Of these, 2.7% were notably hypokalemic before the cleansing procedure.<sup>97</sup> This finding suggests that caution should be employed when administering even isotonic preparations to this particularly vulnerable population of patients, and monitoring of serum electrolytes in this group is highly recommended.

No studies have ever found PEG-ELS-based products to have any great effect on renal function. Some retrospective studies of the possible adverse effects of PEG-ELS and sodium-phosphate-based cathartics on kidney function have shown that the incidence of renal impairment is similar between these two groups (6.8% in the sodium-phosphate group versus 8.7% in the PEG-ELS group),<sup>72</sup> but these results have not revealed cathartics to be a crucial factor for the development of renal impairment.<sup>72,74</sup> However, the definition of markedly impaired renal function differed in these studies.<sup>72,74</sup> Rare cases of allergic reactions,<sup>98,99</sup> as well as one case of pancreatitis,<sup>100</sup> after use of PEG-based cathartics have been published. Safety studies on whether or not the effects of low-volume (2 l) PEG-ELS solutions on fluid and electrolyte balance differ from those of standard (4 l) solutions are limited, but existing data do not suggest any difference.<sup>83,86</sup> Rare events of ischemic colitis after use of bisacodyl, which is sometimes administered as an adjuvant agent with reduced-volume solutions, have been reported.<sup>101,102</sup>

### Magnesium-citrate-based products

Preparations based on magnesium citrate (magnesium oxide and citric acid) are usually administered together with an additional cathartic such as bisacodyl. These products, as well as products based on magnesium citrate and sodium picosulfate, are low-volume hypertonic solutions.<sup>4</sup> Magnesium-based products can be included as an adjuvant in 'dietary and cathartic' regimens used in patients with dietary restrictions such as intake of clear fluids and low-residue foods (foods that leave minimal fecal residue in the colon) for 1–4 days before the procedure.<sup>2</sup>

Magnesium-based products can cause a transient rise in serum levels of magnesium.<sup>103–105</sup> In a study of the effect of magnesium citrate on biochemical parameters, marked alterations in serum levels of sodium, chloride, potassium, urea and magnesium levels were found in the subgroup of elderly patients (aged  $>60$  years). These changes were all asymptomatic and levels remained within the normal ranges.<sup>105</sup> Medications and medical

conditions that affect renal and intestinal function might influence the uptake and elimination of magnesium and thereby predispose patients to developing hypermagnesemia. The clinical condition of patients treated with magnesium-based cathartics who have developed hypermagnesemia can be worsened by further decreases in gut motility and kidney function (through the neuromuscular and cardiovascular adverse effects of high magnesium levels), which can both increase the uptake and impair the clearance of magnesium, thereby exacerbating the hypermagnesemia.<sup>106</sup> Patients with gastrointestinal disorders and/or reduced renal function are likely to be susceptible to these effects.<sup>106</sup>

A small number of cases of severe hypermagnesemia have been reported after use of magnesium-based cathartics in patients with renal impairment and/or bowel dysfunction.<sup>106–108</sup> Furthermore, rare reports of severe hyponatremia have been published.<sup>33,109</sup> One of these cases occurred in an 80-year-old woman without any medications or medical conditions that predisposed to hyponatremia.<sup>109</sup> The other case occurred in a 64-year-old woman with a history of long-term use of thiazide diuretics, which was thought to have possibly contributed to the development of hyponatremia.<sup>33</sup> One study that focused on the effect of magnesium citrate on kidney function did not find any changes in relevant biochemical parameters such as estimated glomerular filtration rate and serum levels of urea, sodium or potassium.<sup>110</sup> None of the studies that investigated possible impairment of renal function after use of PEG-ELS or sodium-phosphate-based products included a group who received magnesium-citrate-based solutions.<sup>66–69,72–75</sup>

Other studies have reported notable effects on blood pressure, body weight and hemoglobin concentration associated with use of magnesium-citrate-based cathartics, with a decrease in body weight of 1.6–2.3 kg and increases in hemoglobin levels of up to 5% (6.5 g/l), which indicates a marked loss of fluid.<sup>111,112</sup> Intravenous administration of a minimum of 2 l of fluid in these studies was recommended to compensate for the dehydrating effect.<sup>111,112</sup>

Substantial changes in electrolyte and mineral levels are observed to an increased extent in elderly patients after the use of magnesium-based cathartics.<sup>105</sup> This association could be explained by an age-related drop in the glomerular filtration rate, impaired homeostatic control of electrolytes and water, reduced gut motility, and the use of medications that have an effect on renal and intestinal function.<sup>106,107,113</sup>

### Future perspectives

The ideal bowel-cleansing preparation—one that combines efficacy with excellent tolerability and only minor adverse effects—remains to be developed. Low-volume magnesium-citrate-based preparations seem to be reasonably safe when used in well-hydrated, young, healthy patients, but a thorough investigation of the potential safety issues of this group of cathartics, as well as of the new low-volume isotonic preparations, is desirable. In particular, the potential influence of these agents on kidney function needs to be further elucidated.

Products based on sodium sulfate are possible low-volume alternatives to sodium-phosphate-based cathartics. These products seem to be minimally absorbed in the intestine (unlike existing low-volume hypertonic cathartics) and, therefore, should not induce supra-physiological serum levels of electrolytes or affect renal function.<sup>114</sup> A small study of the effect of oral sulfate solution on biochemical parameters in patients with renal or hepatic impairment did not find any notable abnormalities in blood chemistry, which suggests that sulfate-based cathartics could be safe even in these populations of vulnerable patients.<sup>115</sup>

Prospective studies of the effects on renal function of sodium-phosphate-based cathartics could be useful in further identifying specific populations of patients at risk (Box 2),<sup>71</sup> as well as attempting to quantify these risks. However, if the potential for renal damage connected to the use of these products is strong, putting these patients at risk by investigating this topic further in prospective, randomized trials would be unethical.

### Recommendations for clinical practice

Hypertonic cathartics (especially sodium-phosphate-based products) can cause clinically important changes in serum levels of minerals and electrolytes and are not recommended in patients with known or possible contraindications (for example, those with comorbidities or taking medications that affect uptake or elimination of sodium-phosphate-based or magnesium-citrate-based products). In patients who are predisposed to the development of water, electrolyte or mineral imbalance PEG-ELS-based solutions are unquestionably the safest option.

Subclinical changes in renal and intestinal function are common in elderly individuals (>55 years of age)<sup>22,70</sup> and electrolyte imbalance, dehydration, and hyperosmolality are observed more frequently in this population,<sup>113</sup> which can pose problems if hypertonic solutions are used. The risks associated with administration of a hypertonic product to these patients can be minimized through routine monitoring of relevant biochemical parameters (for example, serum levels of electrolytes, minerals and creatinine). If necessary, the patient can be admitted to hospital during the bowel-cleansing procedure to ensure a well-hydrated state. Furthermore, sodium-phosphate-based products might cause irreversible kidney damage in elderly patients with previously normal kidney function and should be considered the least favorable choice among the options discussed in this Review. The exact circumstances under which sodium-phosphate-based agents cause renal damage remain unknown, but the available evidence should nonetheless be enough to discourage their routine use for bowel cleansing in patients scheduled for colonoscopy or radiological examination.

The use of PEG-ELS bowel-cleansing preparations rarely leads to any clinically important disturbance of fluid, mineral and electrolyte balance, owing to their isosmolality and nonabsorbability, which makes them a safe alternative to their hyperosmolar counterparts. A disadvantage with the standard PEG-ELS products is

the large volume (up to 4l) that needs to be ingested. A substantial number of patients are unable to ingest such a large amount of fluid in standard preparations.<sup>77-79</sup> Low-volume (2l) solutions might be superior in this regard to the standard (4l) preparations.

As all bowel-cleansing procedures by their nature have the ability to cause clinically notable states of dehydration and electrolyte shifts (owing to vomiting, diarrhea, and inadequate or extensive water intake), sufficient hydration of patients throughout the procedure must be ensured (even when the agent used is osmotically balanced against plasma). In particularly vulnerable patients (that is, elderly patients with relevant comorbidities), routine monitoring of serum electrolytes can be useful, independent of the regimen applied.

### Conclusions

Adequate bowel cleansing is a prerequisite for reliable and safe colonoscopy procedures or colonic radiological examinations. Sodium-phosphate-based cathartics provide effective bowel cleansing with excellent tolerability, but can cause serious adverse events (including metabolic disturbances and irreversible kidney injury). For this reason, PEG-ELS solutions are, therefore, considered a safer option than sodium-phosphate-based cathartics. Isotonic preparations are the safest option, whereas hypertonic solutions should be used with caution, especially in elderly individuals and patients who are prone to developing disturbances in water and electrolyte balance. Magnesium citrate is considered reasonably safe for use in young, adult patients. Monitoring of relevant biochemical parameters, such as serum electrolytes, might be necessary following bowel preparation in elderly patients with relevant comorbidities, independent of the type of cathartic used. Owing to the risk of APN and chronically impaired kidney function that might result from use of sodium-phosphate-based products, routine use of this particular group of cathartics for bowel cleansing should be avoided. Colonic cleansing is not without risks, but awareness of the potential safety issues of the different types of osmotically acting cathartics can reduce the risk of severe adverse events and help tailor regimens for bowel cleansing to each individual patient.

#### Review criteria

PubMed was searched in July 2010 using the following search terms: "cathartics", "magnesium citrate", "polyethylene glycols", and "sodium phosphate" in combination with "colonoscopy" and "adverse effects", "hypermagnesemia", "hyponatremia", "hyperphosphatemia", "hyponatremia", "kidney failure", "renal insufficiency", and "water-electrolyte imbalance". English-language reviews, practical guidelines, letters, editorials, and articles were considered. No publication date restrictions were applied. Subsequently, articles were selected for inclusion in the Review on the basis of their relevance, and additional articles were identified by scanning their reference lists. Other sources of information were the websites of the European Medicine Agency, the FDA, Health Canada and the Cochrane Library databases.

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#### Author contributions

All authors contributed equally to all aspects of this manuscript.