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Adverse drug event of hypokalaemia-induced cardiotoxicity secondary to the use of laxatives: A systematic review of case reports

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Abstract

What is known and objective: The imbalance in serum potassium caused by laxatives can negatively affect the cardiovascular system, leading to life-threatening consequences. Our objective was to evaluate the reported evidence of adverse events related to the cardiac system due to laxative-induced hypokalaemia from case reports.

Methods: A systematic electronic literature search of PubMed, Embase, the Cochrane Library and Science Direct was conducted for the period 1995-2019. In these databases, search terms describing hypokalaemia and cardiotoxicity were combined with the term laxative use.

Results and discussion: Over the 23 years, 27 incidents were identified in 12 countries. There were 19 female and eight male patients, with ages ranging from 1 month to 93 years. The frequency of reported cases according to severity was the following: severe hypokalaemia 48%, moderate hypokalaemia 44.4% and mild hypokalaemia 7.4%. In 70% of patients, the effect of laxative on the heart was typical hypokalaemic electrographic changes, 7.4% showed abnormal changes in cardiac rhythm, whereas in 18.5%, the cardiotoxicity observed was a very serious kind. Two patients died due to severe cardiac effects.

What is new and conclusion: The laxatives—along with the involvement of some other contributing factors—caused mild-to-severe hypokalaemic cardiotoxicity. These factors were non-adherence of the patient to the recommended dosage, laxative abuse, drug-drug and drug-disease interactions, non-potassium electrolyte imbalances and the use of herbal laxatives. We recommend that laxatives and aggravating factors should be taken into account in the assessment of patients with suspected hypokalaemic cardiotoxicity.

KEYWORDS

adverse drug event, cardiotoxicity, hypokalaemia, laxative

1 | WHAT IS KNOWN AND OBJECTIVE

Potassium (K^+) is the most abundant ion present inside the cell.¹ It plays a major role in the regulation of different functions of the body, including the cardiovascular system. Studies have reported that an

intake of 3600-3800 mg of potassium daily is necessary to reduce the risk of heart-related diseases.^{2,3} But, at the same time, the most common electrolyte disturbance diagnosed in clinical settings is hypokalaemia.¹ Hypokalaemia, that is serum potassium ≤ 3.5 mmol/L, occurs in 21% of hospitalized patients and 2% to 3% of outpatients.^{4,5}

It can be of mild (K 3-3.5 mmol/L), moderate (K 2.5-3 mmol/L) or severe (K < 2.5 mmol/L).⁴

The use of medications like laxatives is one of the causes of hypokalaemia.⁴ The misuse or abuse is the main cause of laxative-induced hypokalaemia. However, studies have also reported incidences of hypokalaemia by laxatives in their standard recommended dosage.^{6,7}

The use of laxative by humans stretches back over 2000 years.⁸ A survey conducted in seven countries concluded that 12.3% of the adult population have constipation, of which 16 to 40% use laxatives.⁹ Similarly, 74% of the elderly population in nursing homes use laxatives daily.⁸ Among the users of laxatives, patients suffering from eating disorders constitute the largest group.¹⁰ For instance, in anorexia nervosa, purging behaviours like vomiting, laxative and/or diuretics abuse are noted in about 30% of patients.³

The human body excretes potassium in stool water as the primary electrolyte in the conc. of 70-90 mmol/L, followed by sodium in conc. of 30-40 mmol/L and chloride in 15 mmol/L.⁶ Therefore, patients who use laxatives chronically may experience abnormally low levels of potassium in their serum.⁴ The mechanism is that the laxative-induced faecal excretion of potassium, sodium and water results in hypersecretion of renin, which in turn leads to secondary hyperaldosteronism. Aldosterone stimulates retention of sodium with water and causes further excretion of potassium through both the renal and faecal routes. As a result, the level of potassium in serum declines.^{11,12}

The imbalance in serum electrolytes caused by laxatives can negatively affect the cardiovascular system and can lead to life-threatening consequences. It has been reported that constipation and use of laxative are independent factors for chronic heart diseases, ischaemic stroke and mortality.¹³ Similarly, the hypokalaemia associated with laxatives may lead to changes in heart rhythm and even sudden cardiac death.⁸ At a cellular level, the low serum potassium results in prolongation of resting membrane potential, duration of the action potential and a refractory period, which causes rhythmic changes of the heart.¹ The most common arrhythmic changes induced by low levels of potassium are sinus bradycardia, ventricular tachycardia and torsade de pointes.⁵

The effect of hypokalaemia on the heart can be assessed with the help of electrocardiography (ECG).¹ The most common ECG manifestation of hypokalaemia is the appearance of the U wave.¹⁴ Other changes, like decreased amplitude of T wave, depression of ST interval, T-wave inversions and prolongation of PR interval, may also be observed. It should be noted that hypokalaemia is inversely related to the risk of ECG changes and arrhythmias.⁵

The objective of this systematic review was to evaluate the reported evidence for adverse drug events related to the cardiac system due to laxative-induced hypokalaemia from case reports published between 1995 and 2019.

2 | METHODS

A systematic electronic literature search of PubMed, Embase, the Cochrane Library and Science Direct was conducted between the

period of January 1995 and December 2019. We restricted our search to a specific time to collect targeted data about the laxatives that are currently used.

In databases, search terms describing hypokalaemia and cardiotoxicity were combined with terms for laxative use. We also evaluated the latest issues of related journals for articles over the previous 6 months. The bibliographic search of included studies, recent systematic reviews, Cochrane reviews and meta-analyses for relevant case reports was also checked. The keywords searched were the following:

Laxatives use OR laxatives abuse OR purgatives OR cathartics OR bulk-forming agents OR stool softeners OR surfactant agents OR osmotic agents OR stimulant laxatives OR laxative-senna OR bisacodyl OR chronic constipation OR eating disorder OR anorexia nervosa OR bulimia nervosa

AND

Hypokalaemia OR kaliopenia OR low serum potassium level OR electrolyte imbalance OR electrolyte disturbance

AND

Cardiotoxicity OR cardiopathy OR cardiomyopathy OR cardiac arrest OR cardiac accident OR cardiac arrhythmia OR heart attack OR myocardial infarction OR chronic heart failure OR heart failure OR CHF OR congestive heart failure OR cardiovascular disease.

We scanned all the titles and abstracts of studies identified through our searches and excluded all those that were not according to our selection criteria. We evaluated full-text versions of the remaining case reports to assure their eligibility as to be included in the review. The case reports listing laxative-induced hypokalaemic cardiotoxicity with a specific description of the said phenomenon were selected.

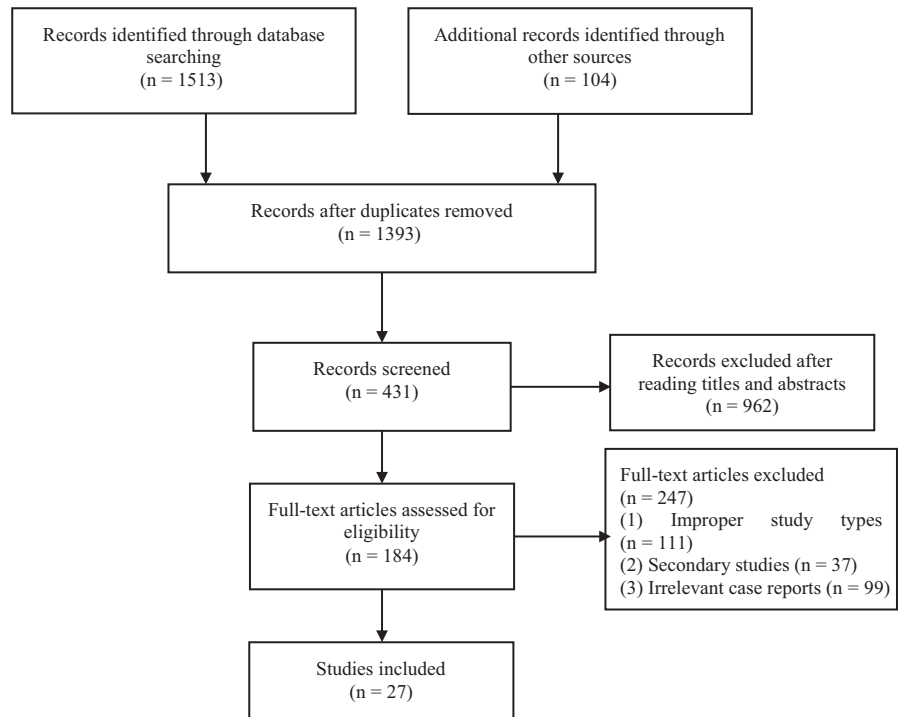
We did not apply any language, age and gender restriction in our searches. We selected the case reports having data related to any form of cardiotoxicity associated with laxative-induced hypokalaemia. The case reports which evaluated drugs not specifically used for constipation were excluded.

3 | RESULTS

The initial records searched from databases were 1,617, out of which 431 were assessed for eligibility. For the final screening, 184 studies were obtained (Figure 1). In the end, 27 case reports were identified over the 24 years in 12 countries, as summarized in (Table 1).^{1,3,11,15-}

³⁸ Most of the case reports were from the United States and the United Kingdom but spread across the whole world.

There were 19 female and eight male patients. Twelve patients were aged above 60 years, 14 aged 12-60 years, and one was a child, that is below 12 years. The age range was 1 month and 18 days to 93 years.

FIGURE 1 Flow chart of the searching and screening studies

The pharmacological classes of laxative noted in our study were of 44% osmotic,^{15,22,25,27-29,31-33,35,36,38} 37% stimulant,^{11,17,22,24,26,29,30,34,37,38} 15% herbal^{16,18,20,34} and 7% stool softeners, respectively.^{17,29} 19% of cases did not specify the name of laxative taken.^{1,3,21,23,25} The frequency of reported cases according to severity was the following: severe hypokalaemia 48%,^{1,3,15,25} moderate hypokalaemia 44.4%,^{9,26,36} and mild hypokalaemia 7.4%.^{37,37} Severe hypokalaemia was most frequently caused by the herbal type of laxative, that is licorice.^{16,18,20} In 17/27 (63%) cases, the reported events were the result of medication error and not due to a typical adverse drug reaction.^{1,3,11,17,19,21,22,24,26-32,36,37}

In 70% of the cases, the effect of the laxative on the heart was of typical hypokalaemic electrographic changes.^{1,3,16-28,30,33,35,36,38} In two cases, that is 7.4% of the total patients, there were abnormal changes in cardiac rhythm due to laxative-associated hypokalaemia.^{29,37} In 18.5%, the cardiotoxicity was of a very serious kind, that is cardiac arrest, cardiac failure, atrial fibrillation and first-degree atrioventricular block with asystole (Figure 2).^{11,15,31,32,34}

The common treatment administered for the management of the signs and symptoms in all the reported patients was the replenishment of electrolytes. Two patients died due to severe cardiac events induced by laxatives.^{15,31}

4 | DISCUSSION

The diagnosis of constipation accounts for one of the top five gastrointestinal diseases.³⁹ In America alone, its prevalence is 50% to 74% in the elderly population, who reported use of laxatives daily.⁴⁰ The mild-to-moderate adverse effects of laxatives have been widely studied, but their lethal effects on the heart, specifically due to their

hypokalaemic property, are poorly understood.⁴¹ For instance, Sumida et al investigated the association of constipation status and laxative use with adverse cardiac effects in a large cohort group of 3,359,653 subjects. But the relationship between laxative-induced hypokalaemia and its effect on the cardiac system was not examined.¹³

We reviewed the reported cases in which the laxatives had injurious consequences to the cardiac system by lowering the serum potassium level. The most common cardiotoxicity results from laxative-induced hypokalaemia were ECG changes.^{1,3,16-28,30,33,35,36,38} These results are in line with the study of Marti et al, who concluded that in 4826 hypokalaemic patients (potassium < 3.5 mmol/L), about two-thirds (69%) had ECG changes.⁴²

Although the main reason for the reported adverse events in our review was laxative-induced hypokalaemia, there were some other factors that also played a role in the induction of these events by aggravating the hypokalaemic crisis. Along with the reported cases, we found two longitudinal studies, with their conclusion that laxative-induced cardiotoxicity was due to multiple factors (Table 2).^{43,44} Similarly, the reasons for the death of two patients in our reported cases were multifactorial, as reported by the authors. For instance, the patient reported by Reumkens et al had a medical history of cardiovascular disease. The other factors were long-standing vomiting and diarrhoea, concomitant therapy with prednisolone and hydrochlorothiazide, and prolonged bowel preparation (5 L), which led to severe hypokalaemia (1.2 mmol/L) and, as a result, cardiac arrest.¹⁵ In the case of the other patient, the reason of death was intestinal necrosis induced by prolonged hypotension and bradycardia resulting from hypermagnesaemia, together with hypokalaemia.³¹ Based on these facts and figures, we have divided the factors contributing to laxative-induced hypokalaemia-induced cardiotoxicity into the following categories (Figure 3).

TABLE 1 Summary of case reports of an adverse cardiotoxic event caused by the hypokalaemic property of laxatives

Case report	Patient and laxative taken	Past/coexisting cardiovascular disease	Concomitant medication that interacts with serum potassium	Serum electrolytes	Effect on the cardiac system (ECG changes)
Reumkens, 2017 ¹⁵	A 72-year-old woman ingested 2 L plus 3 L of low volume PEG within 5 d for colonoscopy	HTN, cerebrovascular event	HCTZ, prednisolone	Hypokalaemia (1.2 mmol/L)	The cardiac arrest resulted from ventricular fibrillation, and the patient died within 24 h of colonoscopy
Yasue, 2007 ¹⁶	A 93-year-old woman took 5 grams of licorice/day for the last 7 y in the form of two herbal medicines	HTN		Hypokalaemia (1.3 mmol/L), hypocalcaemia, hypocholema	Typical hypokalaemic ECG changes
Chin, 1998 ¹⁷	A 50-year-old woman suffering from laxative abuse and uses to take ten tablets/day of phenolphthalein 65 mg/docusate 100 mg.			Hypokalaemia (1.4 mmol/L), hypobicarbonemia	The appearance of U wave
Crean, 2009 ¹⁸	A 71-year-old woman who takes large quantities of licorice daily for its laxative effect	HTN, small myocardial infarction	Bendroflumethiazide, lisinopril	Hypokalaemia (1.6 mmol/L)	Junctional bradycardia with flattened T waves and increased U wave prominence, resulting in a long QT(U) syndrome
Rudolf, 1999 ¹⁹	A 47-year-old man with laxative abuse		Furosemide	Hypokalaemia (1.7 mmol/L)	Slow sinus rhythm
Webster, 2002 ¹	17-year-old girl suffering from purgatives abuse			Hypokalaemia (1.8 mmol/L)	ST depression
Van den Bosch, 2005 ²⁰	A 59-year-old man took 200 g/day of licorice for 4 wk.			Hypokalaemia (1.8 mmol/L), hyperbicarbonemia	Typical hypokalaemic ECG changes
Finsterer, 2014 ²¹	24-year-old woman with chronic ingestion of laxatives since the age of 15 y	Aborted sudden cardiac death due to ventricular fibrillation and hypokalaemia	Furosemide	Hypokalaemia (1.9 mmol/L), hyponatremia, hypocholema	QT prolongation
Gentile, 2012 ³	A 19-year-old girl uses to take a laxative for weight loss.			Hypokalaemia (1.9 mmol/L), Hypocholema, Hyperbicarbonemia	Prolonged QT interval
Merante, 2010 ²²	An 87-year-old woman usually took high doses of about 70 g/day lactulose and sorbitol syrup	HTN, cerebrovascular disease	Valsartan/HCTZ, furosemide, aspirin	Hypokalaemia (1.9 mmol/L), hyponatremia, hypocalcaemia, hypocholema	Sinus rhythm with sporadic supraventricular and ventricular extrasystoles and presence of U wave
Chua, 2018 ²³	A 39-year-old woman with a history of laxative abuse			Hypokalaemia (2.3 mmol/L)	Deep ST-segment depressions and T-wave inversions, ST elevation in augmented vector right, corrected QT interval was prolonged at 534 ms
Krahn, a1997 ²⁴	A 45-year-old woman suffering from bisacodyl abuse			Hypokalaemia (2.4 mmol/L)	Torsades de pointes

(Continues)

TABLE 1 (Continued)

Case report	Patient and laxative taken	Past/coexisting cardiovascular disease	Concomitant medication that interacts with serum potassium	Serum electrolytes	Effect on the cardiac system (ECG changes)
Ho, 2009 ²⁵	A 79-year-old man who ingested four litres of PEG for a colonoscopy	Anaemia, myocardial infarction, left ventricular dysfunction.	HCTZ, budesonide	Hypokalaemia (2.4 mmol/L), hypomagnesaemia	Polymorphic ventricular tachycardia
Sharma, 2017 ²⁶	A 38-year-old woman uses to take phenolphthalein tablets (190 mg each) for last six years as high as 20-40 pills a day due to laxative abuse	Nutritional anaemia		Hypokalaemia (2.5 mmol/L), hypocalcaemia, hypomagnesaemia	ST depression, U waves and QT prolongation
Beaulieu, 2015 ²⁷	A 53-year-old woman took PEG/electrolytes preparation for colonoscopy diluted with 240 millilitres instead of the recommended 1000 millilitres	HTN	Irbesartan, chlorthalidone, potassium chloride	Hypokalaemia (2.5 mmol/L), hyponatremia	Corrected QT interval of 557 ms without conduction anomaly
Filho, 1996 ²⁸	An 84-year woman who ingested 12 fluid ounces of Fleet phospho-soda ^a instead of the prescribed 1½ fluid ounces before a colonoscopy		A1buterol, triamcinolone, aspirin	Hypokalaemia (2.5 mmol/L), hypocalcaemia, hypomagnesaemia, hyperphosphataemia, hypernatremia, hyperchloremia	Non-specific repolarization changes and a prolonged QT interval
Gonzalez, 2018 ²⁹	Male infant of 1 mo 18 d administered sodium picosulphate at high doses for a long time and Micromax ^b at the same time for constipation		Cisapride	Hypokalaemia (2.56 mmol/L), hyponatremia	Bradyarrhythmias
Riley, 1996 ¹¹	60-year-old woman takes 5 tablets/day of phenolphthalein/rhubarb instead of recommended 2 tablets/day to avoid straining at stool following surgery		Medroxyprogesterone	Hypokalaemia (2.6 mmol/L)	Severe cardiac failure
Laqueille, 2013 ³⁰	The 46-year-old woman used bisacodyl to lose weight			Hypokalaemia (2.7 mmol/L)	Ventricular tachycardia with torsade de pointes
Onishi, 2006 ³¹	The 89-year-old man took 34 gm of magnesium citrate for contrast enema	Atrial fibrillation		Hypokalaemia (2.7 mmol/L), hypermagnesaemia	Atrial fibrillation died on the fourth day of admission
Qureshi, 1996 ³²	A 50-year-old woman who ingested approximately 50 gm of Epsom salt (MgSO ₄) diluted with water to relieve constipation			Hypokalaemia (2.7 mmol/L), hypermagnesaemia	First-degree atrioventricular block with non-specific ST-segment changes, prolonged QT, PR interval and asystole developed.

(Continues)

TABLE 1 (Continued)

Case report	Patient and laxative taken	Past/coexisting cardiovascular disease	Concomitant medication that interacts with serum potassium	Serum electrolytes	Effect on the cardiac system (ECG changes)
Ehrenpreis, 1996 ³³	A 65-year-old woman ingested two 1½ ounces doses of Fleet phospho-soda ^a at 12 h apart for a scheduled colonoscopy.	HTN, coronary artery disease		Hypokalaemia (2.8 mmol/L), hyperphosphataemia	Mildly prolonged QT interval
Harada, 2002 ³⁴	84-year-old man ingested Chinese herbal laxative which contains licorice 400 mg/rhubarb 1600 mg TID for 7 d for its laxative effect	Mitral regurgitation, atrial fibrillation	Furosemide, digoxin	Hypokalaemia (2.9 mmol/L)	Exacerbation of heart failure
Escalante, 1997 ³⁵	41-year-old Hispanic women ingested 4 L of PEG/electrolytes and 90 mL of oral saline laxatives during 2 d for colonoscopy			Hypokalaemia (2.9 mmol/L), hypocalcaemia, hypomagnesaemia, hyperphosphataemia	Prolonged QT interval
Kontani, 2005 ³⁶	A 76-year-old woman ingested 34 gm of magnesium citrate as a laxative at one time.			Hypokalaemia (3 mmol/L), hypocalcaemia, hypophosphataemia, hypermagnesaemia	Sinus tachycardia, 1st-degree atrioventricular block, QT prolongation and sinus arrest with a junctional escape rhythm
Dugal, 2007 ³⁷	63-year-old women on 2-6 tablets/day of senna due to laxative abuse	HTN	Furosemide	Hypokalaemia (3.3 mmol/L), hypochloremia, hyperbicarbonemia, hypophosphataemia	Tachyarrhythmia
Hsu, 2008 ³⁸	81-year-old man administered bisacodyl followed by one piece of Fleet enema ^a for colonoscopy	HTN		Hypokalaemia (3.5 mmol/L), hypocalcaemia, hypernatremia, hyperphosphataemia	Prolonged QT interval

Abbreviations: ECG, electrocardiography; HCTZ, hydrochlorothiazide; HTN, hypertension; PEG, polyethylene glycol.

^aMonobasic sodium phosphate/dibasic sodium phosphate.

^bSodium citrate, sodium lauryl sulphacetate and sorbitol.

4.1 | Non-adherence of the patient to the recommended dosage

To achieve a favourable outcome without any adverse effects from a drug, the patient's adherence to the recommended dosage is very important.⁴⁵ The poor adherence or non-adherence of a patient to a drug dosage may lead to mild-to-severe negative effects. A study reported that the poor adherence of participants under study had a significant role in producing detrimental cardiovascular effects by antihypertensive drugs.⁴⁶ Some 14% of the patients in our study did not take the laxative in the recommended dose.^{11,17,22,27-29,31,32,36} For instance, five tablets/day of phenolphthalein/rhubarb was taken, instead of the recommended two tablets/day.¹¹ Similarly, the recommended dose of magnesium citrate is 8.5-17 gm/day,⁴⁷ but 34 gm of magnesium citrate was taken at a time in two case reports.^{31,36} Filho et al reported that the patient took 12 fluid ounces of laxative instead of the prescribed 1½ fluid ounces before a colonoscopy.²⁸ Similarly, the recommended

dilution of polyethylene glycol/electrolytes preparation is in 1000 millilitres, but it was diluted in only 240 mL water, which resulted in its adverse effect.²⁷

4.2 | Laxative abuse

In general population, the prevalence of laxative abuse is reported as 4.18%.⁸ It is an important cause of disturbances in the serum electrolytes and acid-base balance.¹² We reported 12% of patients who were suffering from laxative abuse in our review.^{1,3,19,21,24,26,30,37} The most common laxative abused was bisacodyl,^{24,30} and the most common illness of patients suffering from laxative abuse was an eating disorder.^{1,3,21,37}

4.3 | Drug-drug interactions

The interaction of laxatives with other drugs, which also interferes with the levels of potassium in the serum, plays a synergistic role in laxative-induced hypokalaemic cardiotoxicities.⁴⁸ The most important of these interactions is with some classes of diuretics.⁴⁹

In 23% of our cases, there were interactions between laxatives and other serum potassium-lowering drugs. The most common drug (5 out of 27 case reports) with which the laxative interacted was furosemide, which belongs to the pharmacological class of loop diuretics.^{19,21,34,37} Another common diuretic (3 out of 27 case reports) was hydrochlorothiazide^{15,22,25} followed by one patient with bendroflumethiazide therapy.¹⁸ The drugs that belong to the group of glucocorticoids and β2 agonists are also associated with low serum potassium levels.⁴⁸ We noted four out of 27 case reports in which the patient used drugs of these classes as the concomitant medication.^{11,15,25,28}

There is an inverse relation of hypokalaemia with digoxin. A low level of serum potassium increases the risk of digoxin toxicity.⁵⁰ Therefore, in the case in which a patient used digoxin as the concomitant drug with

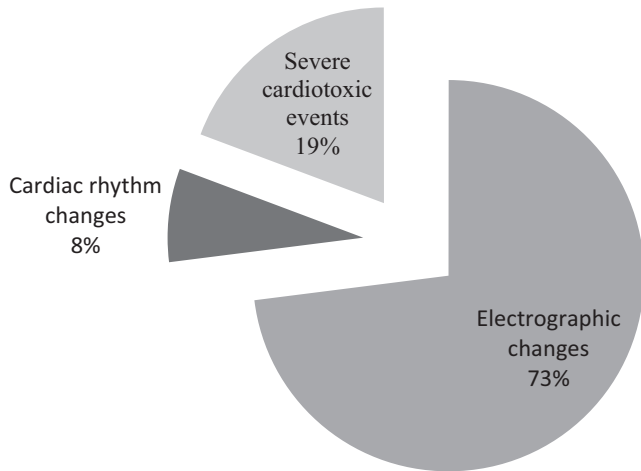


FIGURE 2 Reported adverse drug events of hypokalaemia-induced cardiotoxicity secondary to the use of laxatives

TABLE 2 Summary of two longitudinal studies detailing the hypokalaemic effect of laxatives on the cardiovascular system

Study	Participants included	Laxative taken	Serum electrolytes	Effect on heart	Conclusion
Huang, 2015 ⁴³	Total of 1755 participants aged 45-65 y divided into groups of 1099 (experimental) and 656 (control).	Oral administration of 2 bottles (45 mL each) of oral sodium phosphate, 12 h apart for the procedure of colonoscopy.	Serum potassium and calcium were lower, whereas serum sodium and phosphate were higher in experimental group as compared to the control group.	Lower HRV in experimental group as compared to control group.	Lower HRV in experimental group might be related to an electrolyte imbalance that was caused by the bowel preparation.
Meyers, 1990 ⁴⁴	A total of 11 patients age 17-54 y, of which 9 patients were followed for more than one year	Chronic laxative abuse	All were markedly hypokalaemic. Hypocalcaemia was present in 4 patients and hypomagnesaemia in 6 patients. In addition, 4 out of 7 patients have hypophosphataemia.	Left ventricular gallop, pulmonary oedema and dyspnoea. Right ventricular dysfunction in two patients.	Laxative abuse produced metabolic derangement including electrolyte imbalances.

Abbreviation: HRV, heart rate variability

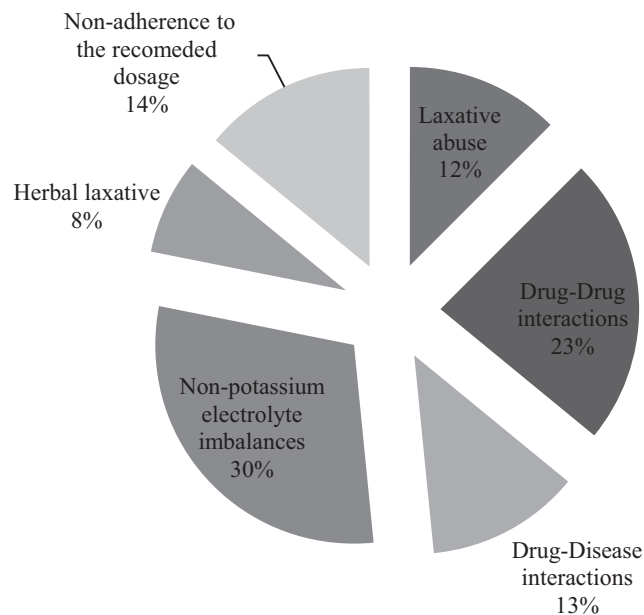


FIGURE 3 Factors contributing to laxative-induced hypokalaemic cardiotoxicity

laxative, this may be one of the reasons for the production of a serious cardiotoxic reaction.³⁴ Similarly, in one case, the author reported that the electrolyte imbalance and its subsequent adverse effects in the patient under study were due to an interaction between cisapride and stimulant laxatives, administered at a higher dose for a long time.²⁹

Interestingly, in four cases the concomitant medications taken by the patients were proven to increase the serum potassium level,⁴⁶ but in our reported cases these medications did not produce any significant effect to counteract the severe hypokalaemic effect of laxatives.^{18,22,27,28}

4.4 | Drug-disease interactions

The coexisting medical condition of a patient has been shown to be associated with adverse drug events due to drug-disease interaction.⁵¹ For instance, the past/coexisting diseases of the cardiac system make the heart prone to the adverse hypokalaemic event.⁵² Therefore, it was one of the factors which increases the possibility of laxative-induced cardiotoxicity in our reported cases.^{15,18,21,22,25,31,33,34}

4.5 | Non-potassium electrolyte imbalances

Besides potassium, our body also needs a balance of other electrolytes. Any change in the serum concentration of these electrolytes results in the appearance of unwanted effects and ECG changes.⁵³ We have reported seven cases in which the primary electrolyte imbalance for the appearance of side effects was hypermagnesaemia, hyperphosphataemia and hyponatremia, together with hypokalaemia. The laxatives which contain mineral elements in their composition—like magnesium

oxide, magnesium citrate and sodium phosphate—were the primary cause of non-potassium electrolyte imbalances.^{27,28,31,33,35,36,38} In eleven cases, there were changes in the serum concentration of electrolytes other than potassium, but these changes were not significant enough to cause serious cardiac effects.^{3,16,17,19,21,22,25,26,29,33,37} However, in nine cases low serum potassium was the only electrolyte responsible for cardiotoxic signs and symptoms.^{1,11,15,18,19,23,24,30,34}

4.6 | Use of alternative herbal laxatives

Complementary and alternative therapies for constipation are commonly used.⁵⁴ The frequently observed problem with alternative herbal therapy is the lack of authentic data regarding their safety issues due to the lack of proper regulations. This increases the chance of the occurrence of adverse effects with highly potent herbal laxatives.⁵⁵ Besides other pharmacological properties, *Glycyrrhiza glabra* (Licorice) is also used as a herbal laxative, and its most important side effect is hypokalaemic-induced secondary disorders.⁵⁶ In our review, 8% of patients suffered from licorice, rhubarb and senna-induced hypokalaemic cardiotoxicity which they took for their laxative effect.^{16,18,20,34,37}

4.7 | Limitations

Case reports are the only source to report the most relevant and rare adverse events of any drug, but in scientific research, which is based on solid evidence, they are not at the top of the list. However, we took this work as a starting point to highlight the adverse drug reaction of laxative-induced hypokalaemic cardiotoxicity. Therefore, we expect more detailed clinical studies specifically designed to work on the said topic.

In 26% of our reported cases,^{16,19,20,22,27,35,38} the author described the negative effect of laxative on multiple organs, that is not specifically on the cardiac system. However, due to our specific study's scope, we did not include the effect of laxatives on organs other than the heart. Similarly, the concomitant use of other hypokalaemic agents, like diuretics or corticosteroids, resulted in the adverse drug reaction by the combined effect of all hypokalaemic agents instead of laxatives alone in some case reports.

5 | WHAT IS NEW AND CONCLUSION

In summary, we conclude that laxatives, in conjunction with other factors, cause hypokalaemia-induced cardiotoxicity that may be of a mild-to-severe type. These contributing factors make the patient more susceptible to the hypokalaemic property of laxatives. The common factor responsible was medication error, like non-adherence of the patient to the recommended dosage and laxative abuse. Other

factors were drug-drug interactions, drug-disease interactions, non-potassium electrolyte imbalances and use of herbal laxatives lacking valid safety data. Therefore, we recommend that laxatives along with other aggravating factors should be taken into account for the patient in which hypokalaemic cardiotoxicity is suspected.

CONFLICT OF INTEREST

None.

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