

Bisacodyl and ischaemic colitis

Introduction

Bisacodyl, is a locally acting laxative indicated for *constipation* and *bowel preparation before diagnostic tests or surgery*. The drug is available in the Netherlands as an enteric-coated tablet and as a suppository. After hydrolysis, bisacodyl stimulates the mucosa of the colon, resulting in increased colonic peristalsis and accumulation of water and electrolytes in the colonic lumen. This stimulates defaecation, reduces transit time and softens the stool [1]. Bisacodyl is available as an over-the-counter drug in pharmacies and drugstores, but can also be prescribed by health care professionals. Bisacodyl was granted marketing authorization in the Netherlands in 1966 as Dulcolax® and is nowadays available as various (generic) brands.

Ischaemic colitis is a type of colitis that results after hypoperfusion in blood supply below the metabolic needs of the colon [2]. This results in colonic mucosal ulceration, inflammation and haemorrhage. Patients can present with abdominal pain, haematochezia and diarrhoea [3]. The scale of injury is determined by the duration and severity of the hypoperfusion. Ischaemic colitis can have numerous causes and risk factors, including various arterial and venous diseases, trauma, surgical procedures (including colonoscopy), hypoperfusion, colonic obstruction, age, gender, long-distance running and iatrogenic causes including bowel preparation media for colonoscopy [2, 4, 5].

Reports

In the period from 22 February 2018 until 21 September 2023 the Netherlands Pharmacovigilance Centre Lareb received two reports of ischaemic colitis in association with the use of bisacodyl [6]. In both cases, bisacodyl was used as bowel preparation for colonoscopy. First signs of ischaemic colitis appeared within hours after ingestion of one single dose of bisacodyl.

Case A (NL-LRB-00270815)

This spontaneous report concerns a woman aged 60-70 years that experienced ischaemic colitis after a sole ingestion of two tablets of bisacodyl 5 mg. Bisacodyl was used as bowel preparation for colonoscopy. Colonoscopy was performed in the context of the national colorectal cancer screening program, because the woman had a positive immunochemical faecal occult blood test (iFOBT). The woman experienced severe abdominal pain with vomiting the night after the ingestion of bisacodyl. After two days, ischaemic colitis was identified during colonoscopy and confirmed with pathology. The woman has congenital long QT syndrome, but no history of colitis and signs of vascular diseases were absent. No other laxatives or concomitant drugs were reported. The woman recovered after a week.

Case B (NL-LRB-00912033)

This spontaneous report concerns a man aged 60-70 years that experienced ischaemic colitis after ingestion of bisacodyl 5 mg for two consecutive days. Bisacodyl was used as bowel preparation for an elective colonoscopy. The first signs of ischaemic colitis appeared hours after the ingestion of the first tablet. Ischaemic colitis was identified during colonoscopy. The reporter stated that other causes were excluded. The man also used macrogol and electrolytes as a concomitant drug. The patient recovered after five days.

Other sources of information

SmPC

'Colitis' is mentioned as a side effect in the Dutch SmPCs of 7 out of 15 registered products of bisacodyl, namely:

1. Dulcolax maagsapresistente tabletten 5 mg, maagsapresistente tabletten [1]
2. Dulcolax zetpillen 10 mg, zetpillen [7]
3. Leidapharm Laxeertabletten Bisacodyl 5 mg, maagsapresistente tabletten [8]
4. Kruidvat laxeertabletten bisacodyl 5 mg, maagsapresistente tabletten [9]
5. Trekpleister laxeertabletten bisacodyl 5 mg, maagsapresistente tabletten [10]
6. Bisacodyl laxeertabletten Sanias 5 mg, maagsapresistente tabletten [11]
7. Bisacodyl laxeertabletten Sanias 5 mg, maagsapresistente tabletten [11]

The SmPCs state that colitis was not reported in clinical studies. The frequency 'rare' was calculated based on the total amount of treated patients, in agreement with the EU SmPC guideline ($3/3368 = 0.0089$, which corresponds with 'rare'). However, colitis has not been specified.

Literature

Several case reports and case series describe ischaemic colitis associated with bisacodyl use attributed to colonoscopy and bowel preparation for colonoscopy (Table 1). In the majority of cases, the first symptoms of ischaemic colitis appeared within hours after administration of bisacodyl. In two cases, ischemic colitis was diagnosed two and six days after colonoscopy respectively. In two cases there was a positive rechallenge. Risk factors for ischaemic colitis were present in most cases, including chronic constipation, cardiovascular disease, colonoscopy, abdominal surgery, laxative abuse and drugs associated with the onset of ischaemic colitis, such as macrogol.

Table 1: Literature cases of ischaemic colitis and bisacodyl

Reference	Patient sex, age	Indication for bisacodyl use	Time to onset	Time to recovery	Rechallenge
Ajani et al. [3]	F, 54Y	Chronic constipation Laxative therapy prior to hip surgery	6 hours	10 days	Not reported
Baudet et al. [12]	M, 68Y	Bowel preparation for follow-up colonoscopy (1Y after polyp removal)	2 hours	Not reported	Positive rechallenge, (2x)
Shamatutu et al. [13]	F, 57Y	Bowel preparation for colonoscopy for a positive iFOBT	2 days after colonoscopy	6 days	Not reported
	F, 69Y	Bowel preparation for surveillance colonoscopy	6 days after colonoscopy	7 days	Not reported
Tomer et al. [14]	F, 66Y	Bowel preparation for elective colonoscopy	6 hours	Not reported	Not reported
	F, 66Y	Bowel preparation for elective colonoscopy	Few hours	Not reported	Not reported
	M, 73Y	Bowel preparation for elective colonoscopy	Few hours	Not reported	Not reported
	M, 70Y	Bowel preparation for elective colonoscopy	6 hours	Not reported	Not reported
	F, 53Y	Bowel preparation for elective colonoscopy	Few hours	Not reported	Not reported
	F, 42Y	Bowel preparation for elective colonoscopy	Few hours	Not reported	Not reported
	M, 67Y	Bowel preparation for elective colonoscopy	Few hours	Not reported	Not reported
	F, 69Y	Bowel preparation for elective colonoscopy	Few hours	Not reported	Not reported
Theorode et al. [15]	F, 69Y	20 year history of laxative abuse	Unknown	Unknown	Not reported
Lopez et al. [16]	F, 33Y	Constipation	6 hours	2 days	Not reported
	M, 19Y	Constipation	Few hours	2 days	Not reported
Vaizman et al. [17]	M, 56Y	Bowel preparation for colonoscopy	Few hours after administration of bisacodyl and polyethylene glycol preparation	Not reported	Not reported
	F, 78Y	Bowel preparation for elective colonoscopy	Few hours after administration of bisacodyl and polyethylene glycol preparation	Not reported	Not reported
Dholakia et al. [18]	F, 37Y	Bowel preparation for colonoscopy for evaluation of rectal condylomata	One day after administration of bisacodyl and polyethylene glycol preparation	Not reported	Positive rechallenge
Woreta et al. [19]	F, 71Y	Constipation	Few hours	Not reported	Not reported

Behzadi et al. [20]	F, 64Y	Bowel preparation for colonoscopy for colorectal cancer screening	Few hours	Several days	Not reported
---------------------	--------	---	-----------	--------------	--------------

F: Female; M: Male; Y: Years. Two additional case reports based on literature listed in Eudravigilance could not be found and are not added to the Table 1 [21, 22].

Moreover, a database study by O'Reilly et al. revealed that use of four bisacodyl tablets in addition to MiraLax/Gatorade preparation prior to colonoscopy resulted in a 7-fold increased incidence of ischemic colitis [23].

Other databases

Table 2: Reports of ischaemic colitis (PT) associated with bisacodyl in the Lareb, Eudravigilance and WHO database [6, 24, 25].

Database	Number of reports	ROR (95% CI)
Lareb	2	-
Eudravigilance*	42	40.5 [29.8-55.0]
Vigibase*	46	57.5 [43.0-72.0]

*Including the reports received by Lareb.

In Eudravigilance, 42 reports were received of ischaemic colitis in association with bisacodyl [24]. These include 21 cases that are based on literature cases [3, 12, 14, 16-22]. Some of the reports derived from literature are duplicates.

Prescription data

Table 2: Number of patients using bisacodyl in the Netherlands between 2018 and 2022 based on prescription data [26].

Drug	2018	2019	2020	2021	2022
A06AB02 Bisacodyl	55,296	57,697	49,306	53,191	51,501

It is unknown how many patients used bisacodyl as an over-the-counter drug.

Mechanism

Bisacodyl is a locally acting laxative from the diphenylmethane derivatives group [7]. The increased colonic motility causes higher pressure within the colon, which can hinder and even disrupt blood flow. This can result in ischaemic colitis [12]. Another hypothesis is that ischaemia can occur when the elevated oxygen demand due to the increased colonic motility cannot be met.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received two reports of ischaemic colitis associated with the use of bisacodyl. In both cases, the first signs of ischaemic colitis appeared within several hours after intake of bisacodyl. Several similar cases are presented in literature and Eudravigilance. A possible mechanism for ischaemic colitis attributed to bisacodyl use is that bisacodyl increases colonic peristalsis. This may increase colonic pressure and thereby hinder or even disrupt blood flow, resulting in colonic ischaemia. Another hypothesis is that ischaemia can occur when the elevated oxygen demand due to the increased colonic motility cannot be met. Since ischaemic colitis has multiple risk factors, it is possible that patients with these risk factors are predisposed to the effects of bisacodyl, which may increase the risk of ischaemic colitis in these patients. As an example, the patient in case B used macrogol and electrolytes as a concomitant drug, which can reportedly increase the risk of ischaemic colitis in patients with risk factors of ischaemic colitis or when used in combination with bisacodyl [27].

Even though 'colitis' has already been described as a potential adverse drug reaction in various SmPCs of bisacodyl, it is warranted to elucidate that type ischaemic subtype of colitis can also occur after bisacodyl use. After all, ischaemic colitis can develop within several hours after intake of a single dose of bisacodyl and can have serious consequences for patients if not recognized in time. In conclusion, attention for this potential adverse drug reaction is warranted.

References

1. Dutch Summary of Product Characteristics Dulcolax® [updated 15-07-2023] [Available from: https://www.geneesmiddeleninformatiebank.nl/smpc/h03843_smpc.pdf].
2. Azer SA SY. Colitis. In: Publishing S, editor. StatPearls [Internet]. Treasure Island (FL)2024.
3. Ajani S, Hurt RT, Teeters DA, Bellmore LR. Ischaemic colitis associated with oral contraceptive and bisacodyl use. BMJ Case Rep. 2012;2012.

4. Washington C, Carmichael JC. Management of ischemic colitis. Clin Colon Rectal Surg. 2012;25(4):228-35.
5. Brandt LJ, Feuerstadt P, Longstreth GF, Boley SJ. ACG clinical guideline: epidemiology, risk factors, patterns of presentation, diagnosis, and management of colon ischemia (CI). Am J Gastroenterol. 2015;110(1):18-44; quiz 5.
6. Netherlands Pharmacovigilance Centre Lareb Database [31-01-2024].
7. Dutch Summary of Product Characteristics Dulcolax® suppository [updated 15-07-2023] [Available from: https://www.geneesmiddeleninformatiebank.nl/smpc/h03844_smpc.pdf.
8. Dutch Summary of Product Characteristics bisacodyl Leidapharm [updated 15-06-2023] [Available from: https://www.geneesmiddeleninformatiebank.nl/smpc/h52273_smpc.pdf.
9. Dutch Summary of Product Characteristics bisacodyl Kruidvat [updated 15-06-2023] [Available from: https://www.geneesmiddeleninformatiebank.nl/smpc/h52273_smpc.pdf.
10. Dutch Summary of Product Characteristics bisacodyl Trekpleister [updated 15-06-2023] [Available from: https://www.geneesmiddeleninformatiebank.nl/smpc/h52273_smpc.pdf.
11. Dutch Summary of Product Characteristics bisacodyl Sanias [updated 15-06-2023] [Available from: https://www.geneesmiddeleninformatiebank.nl/smpc/h52273_smpc.pdf.
12. Baudet JS, Castro V, Redondo I. Recurrent ischemic colitis induced by colonoscopy bowel lavage. Am J Gastroenterol. 2010;105(3):700-1.
13. Shamatutu C, Chahal D, Tai IT, Kwan P. Ischemic Colitis after Colonoscopy with Bisacodyl Bowel Preparation: A Report of Two Cases. Case Rep Gastrointest Med. 2020;2020:8886817.
14. Tomer O, Shapira Y, Kriger-Sharabi O, Mawasi N, Melzer E, Epshtein J, et al. An Israeli national survey on ischemic colitis induced by pre-colonoscopy bowel preparation (R1). Acta Gastroenterol Belg. 2022;85(1):94-6.
15. Theodore BC, Foulkrod A, Fujikawa P, Patel K. Ischemic Colitis Secondary to Olanzapine and Clonidine Use in a Patient With a History of Laxative Abuse. Cureus. 2023;15(3):e36605.
16. Lopez Morra HA, Fine SN, Dickstein G. Colonic ischemia with laxative use in young adults. Am J Gastroenterol. 2005;100(9):2134-6.
17. Vaizman K, Li J, Iswara K, Tenner S. Ischemic Colitis Induced by the Combination of Bisacodyl and Polyethylene Glycol in Preparation for Colonoscopy: 414. Official journal of the American College of Gastroenterology | ACG. 2007;102:S267.
18. Dholakia A, Islam K. Colonic Ischemia in a Young Patient: Who To Blame?: 948. Official journal of the American College of Gastroenterology | ACG. 2010;105:S343.
19. Woreta T, Victor D. A Case of Acute Ischemic Colitis Following Laxative Use: 1210. Official journal of the American College of Gastroenterology | ACG. 2012;107:S482.
20. Behzadi J, Kanuru R, Pfeil S. Colonoscopy Prep-Induced Ischemic Colitis: 348. Official journal of the American College of Gastroenterology | ACG. 2015;110:S152-S3.
21. Moskovitz M SD, Zaleski M. Ischemic colitis: female bias and more common than you think. Am J Gastroenterol. 2006;101(9).
22. Limido E GM, Guicciardi M, De Marco A, Misitano P, Sala D. Ischemic colitis induced by colonoscopy preparation. Report of a case. Dig Liver Dis. 2014(46).
23. O'Reilly P BL, Vargo PM. High Dose Bisacodyl As Part of a Colonoscopy Preparation May Cause Colon Ischemia. American Society for Gastrointestinal Endoscopy; April 20092009.
24. Eudravigilance [31-01-2024]. Available from: <http://bi.eudra.org> (access restricted).
25. WHO Vigibase [09-02-2024]. Available from: <https://vigilyze.who-umc.org/> (access restricted).
26. GIP Database - Drug Information System of the Dutch Health Care Insurance Board [31-01-2024]. Available from: https://www.gipdatabank.nl/databank?infotype=g&label=00-totaal&tabel=B_01-basis&geg=gebr&item=A06AB02.
27. Dutch Summary of Product Characteristics Pleinvue® [updated 28-04-2023] [Available from: https://www.geneesmiddeleninformatiebank.nl/smpc/h120195_smpc.pdf.

This signal has been raised on April 22, 2024. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbq-meb.nl