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EDITORIAL

Medical influences, surgical outcomes: Role of common medications on the risk of perforation from untreated diverticular disease

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Abstract

Numerous drugs, largely used in the wards or at home, have a significant influence on patients with untreated diverticular disease. The consequences can be disastrous, may require an emergency operation, postoperative intensive care, and overall influence the patient's length of stay and the final outcomes. Bearing these considerations in mind the routine or chronic administration of pain-killers, steroids and non-steroidal anti-inflammatory should be balanced in patients with known diverticular disease as it normally happens with other conditions potentially affected by these drugs (*i.e.*, peptic ulcer disease or chronic obstructive pulmonary disease). This is even more important in the old and frail patient where an eventual surgical treatment may not always be possible.

Key words: Perforation; Diverticular disease; Medications; Drugs; Risk factor

Core tip: Numerous drugs have an influence on patients with untreated diverticular disease. This is even more important in the old and frail patient where an eventual surgical treatment may not always be possible.

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INTRODUCTION

Colonic diverticular disease is a common disease with a prevalence that increases with aging (65% by 80 years)[1]. A minority of patients (15%) experience severe complications. Pseudodiverticula are the most common and usually composed of the mucosal and submucosal layers. Therefore, they act as locus minoris resistentiae on the bowel wall and increase the predisposition towards perforation. Abscess formation, purulent or fecal peritonitis are the most common consequences of perforation and are associated with a high morbidity, intensive care requirements, prolonged hospital admissions and increased mortality (12%-36%)[1,2]. Conditions that predispose to an increased intraluminal pressure or reduced resistance of the diverticular mucosa can lead to perforation[1]. In this view, excessive colonic segmentation may increase intracolonic pressures and the stress forces acting on the diverticular mucosa[3], while impairment of the mucosal barrier of the diverticulum may lead to mucosal weakening through modifications of the secretion of protective mucus[3]. Numerous drugs have such effects on patients and therefore increase the risk of perforation from colonic diverticula. The association of perforated diverticular disease with these drugs has been described in various studies. The diverticular disease is usually untreated at the

time of perforation and sometimes even undiagnosed as some patients are unaware of its presence until the perforation manifests.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used classes of medications. On large surveys 17% of the general population assumes NSAIDs as chronic anti-inflammatory medications or for long-term pain control, and prescriptions for generic ibuprofen, naproxen and selective inhibitors of the cyclooxygenase 2 enzyme exceed every year the cost of billions[4]. A description of the pathophysiological and clinical effects of NSAIDs on the normal colonic mucosa is essential for a proper understanding of their influence on segments affected by diverticular disease. NSAIDs manifest their harmful action on the mucosa through the inhibition of the COX enzymes[5,6]. Cyclooxygenase (COX)-1 normally synthesizes protective prostaglandins while COX-2 is pro-inflammatory. In the first case, the lack of protective prostaglandins weakens the diverticular mucosa to noxious agents, in the second the inflammatory reaction in cases of microperforation of the diverticula is diminished and therefore the ability to contain the extracolonic contamination[5,6].

NSAIDs have long been associated with complications in the upper gastrointestinal tract. More recently, adverse effects upon the small and large intestine have become more recognized and reported. Individuals who regularly take NSAIDs have a significantly higher incidence of lower intestinal lesions when compared with non-NSAID takers, and such risk increases with the duration of NSAIDs ingestion. NSAIDs have been associated with a particular form of colitis[7] that present with diarrhoea, anemia and non specific abdominal pain[8]. Endoscopy revealed flat ulcers in the entire colon similar to ulcerations and erosions found in the small bowel[8,9]. The median time from onset of symptoms to diagnosis was 1.8 years (range, 0.0-11.5 years)[8] and prolonged use of NSAIDs increased the risk of mucosal damage more than the short use[7]. In portions of large bowel not affected by underlying diseases numerous cases of strictures were also reported[10-15]. Such lesions appeared on endoscopy as concentric "diaphragm-like" strictures similarly to those described in the small bowel[8,9]. Finally, NSAIDs-induced perforations have been described especially in the cecum[16-19], usually caused by more distal strictures[10,11].

NSAIDs are frequently used to treat concomitant arthritic or cardiovascular diseases and not necessarily prescribed to alleviate symptoms in patients with diverticular disease[20]. Most patients are even unaware of the presence of diverticular disease until the perforation occurred[20]. In segments of the colon affected by diverticular disease NSAIDs increased the risk of bleeding[21-24] and perforation of diverticula. Six retrospective case-controls studies have analysed the association between perforated diverticular disease and NSAIDs, making it the most studied class of drugs with regards to such association (Table 1)[20,25-29]. The incidence of NSAIDs in patients with perforated diverticular disease was compared with healthy controls[20,25,27] or with patients having simple non-perforated diverticular disease[20,26,28]. Overall, NSAIDs were present in 10% of patients with perforated diverticular disease (118/1182) and 3.8% of controls (391/10385), sub-classified in 3.4% in healthy people (341/9950) and 11.5% in non-perforated diverticular disease (50/435). When compared with healthy controls, OR for the use of NSAIDs in patients with perforations was 1.5 (95%CI: 1.01-2.3) for Humes *et al*[27], 1.8 (95%CI: 0.96-3.4) for Mpofu *et al*[25], 2.1 (95%CI: 1.3-3.4) for Goh *et al*[20]. When compared to simple diverticular disease OR were higher: 3.6 (95%CI: 1.5-8.4) for Piekarek *et al*[28], 4.6 (95%CI: 1.7-12.5) for Goh *et al*[20], 4.8 (95%CI: 1.6-14.8) for Corder[26]. ORs results are consistent among studies and indicate a higher presence of NSAIDs in patients experiencing perforation compared to both control groups. Interesting, higher ORs are present when perforated patients are compared to non-perforated ones as if the presence of diverticula increase the predisposition to perforation from NSAIDs compared to healthy subjects.

CORTICOSTEROIDS

Corticosteroids are potent anti-inflammatory and immunosuppressive drugs used for a number of common and rare diseases. It is estimated that up to 0.9% of the general population receives oral administrations of corticosteroids, and 22% of these patients continue the treatment for longer than 6 mo. The most frequent indications are respiratory diseases (80%) followed by pathologies of the musculoskeletal system (12%) and the skin (10%)[30]. Arthropathies are most likely to require a chronic treatment compared to the other indications[30].

The relationship between chronic rheumatic diseases, long-term use of corticosteroids and complications from diverticular disease has long been investigated from different perspectives. In a large study on patients with rheumatoid arthritis corticosteroids were associated with perforations of the lower gastrointestinal tract and death[31]. At the same time, patients with chronic rheumatic conditions experienced a six-fold increase of death from complicated diverticular disease than the general population[32]. The long-term use of corticosteroids has been described in chronic rheumatic patients suffering from perforated diverticular disease[33-37]. Sporadic cases of diverticular perforation have also been reported in patients following neurosurgery operations[38], transplants[39-43] or under steroidal treatment for asthma and cancer[44]. In some patients the diverticular disease was even unsuspected until the fatal event happened[34,38].

Corticosteroids may increase the likelihood of clinically-manifested diverticular perforations by both etiologic and contributing mechanisms. Steroidal use inhibits

Table 1 Case-controls studies investigating the association of non-steroidal anti-inflammatory drugs, steroids, opioids, calcium channel blockers and perforated diverticular disease

Author	Country	Drugs	Patients (*n*)	Control group (*n*)	OR
Goh *et al*[20]	United Kingdom	NSAIDs	20	HC (600), DD (125)	2.1 (95%CI: 1.3-3.4) for HC 4.6 (95%CI: 1.7-12.5) for DD
Mpofu *et al*[25]	United Kingdom	NSAIDs	64	HC (320)	1.8 (95%CI: 0.96-3.4)
Corder *et al*[26]	United Kingdom	NSAIDs	-	DD	4.8 (95%CI: 1.6-14.8)
Humes *et al*[27]	United Kingdom	NSAIDs	899	HC (8980)	1.5 (95%CI: 1.01-2.3)
Piekarek *et al*[28]	Sweden	NSAIDs	54	DD (183)	3.6 (95%CI: 1.5-8.4)
Mpofu *et al*[25]	United Kingdom	Steroids	64	HC (320)	31.9 (95%CI: 6.4-159.2)
Corder *et al*[26]	United Kingdom	Steroids	-	DD	13.2 (95%CI: 1.81-96.5)
Humes *et al*[27]	United Kingdom	Steroids	899	HC (8980)	2.7 (95%CI: 1.6-4.6)
Piekarek *et al*[28]	Sweden	Steroids	54	DD (183)	28.3 (95%CI: 4.8-165.7)
Humes *et al*[27]	United Kingdom	Opioids	899	HC (8980)	2.2 (95%CI: 1.6-3.0)
Piekarek *et al*[28]	Sweden	Opioids	54	DD (183)	4.5 (95%CI: 1.7-12.2)
Morris *et al*[3]	United Kingdom	Ca^{2+}	120	HC (480)	0.4 (95%CI: 0.2-0.9)
Humes *et al*[27]	United Kingdom	Ca^{2+}	899	HC (8980)	0.54 (95%CI: 0.24-1.24)
Piekarek *et al*[28]	Sweden	Ca^{2+}	54	DD (183)	0.14 (95%CI: 0.02-0.95)

NSAIDs: Non-steroidal anti-inflammatory drugs; Ca^{2+}: Calcium-channels blockers; HC: Healthy control; DD: Non-perforated diverticular disease.

the cyclo-oxygenase enzyme in the gut that normally produces prostaglandins with local protecting effects[1]. Prostaglandins enhance the gut mucosal barrier by stimulating the secretion of mucin and bicarbonate and increasing the local blood flow[45]. Their absence predisposes the mucosa to the effects of noxious agents such as bacteria and toxins[45]. Additionally, corticosteroids are potent immunosuppressant that masks the immune response to local inflammations and small perforations. The ability of the body to contain small perforations is therefore impaired, their local effects are therefore increased and even the classic clinical symptoms may be masked until advanced contaminations eventually become evident[46].

Four case-controls studies have investigated so far the association of perforated diverticular disease and corticosteroids (Table 1)[25-28]. In two studies controls were healthy people[25,27] and in the rest non-perforated diverticular disease[26,28]. Overall, corticosteroids were present in 4.4% of patients with perforated diverticular disease (49/1112) and 0.7% of controls (71/9560), subclassified in 0.7% in healthy people (68/9300) and 1.2% in non-perforated diverticular disease (3/260). All studies confirmed an increased risk of perforation with their use that was 2.7 (OR = 1.604.6) according to Humes *et al*[27], 13.2 (RR, 95%CI: 1.81-96.5) for Corder[26], 28.3 (OR, 4.8-165.7) for Piekarek *et al*[28], and 31.9 (OR, 95%CI: 6.4-159.2) for Mpofu *et al*[25]. However, a more careful analysis shows that the risk increase presented by Humes *et al*[27] is markedly lower than those reported by the other authors[25,26,28]. No direct comparison of the corticosteroids incidences is possible for the control groups because of the above-mentioned heterogeneity among studies (two analyse healthy people and two non-perforated diverticular diseases). Still, case groups present similar patients with perforated diverticular disease in all four studies and therefore incidences can be directly compared. In the study of Humes *et al*[27] only 2.2% (20/899) of perforated patients use corticosteroids compared to 10%-17% reported by the others (10/64 = 16%, 10/95 = 10.5%, and 9/54 = 17%)[25-28]. This could explain the lower increase in the risk conferred by corticosteroids reported by Humes *et al*[27] compared to the others. The main difference noted among these studies is that the report of Humes is based on a nationwide database prospectively-maintained by local general practitioners (General Practice Research Database, United Kingdom). This database has provided a larger number of patients than any other local-based study, possibly giving more reliable epidemiological figures (*n* = 8980 controls, *n* = 890 cases).

OPIOIDS

Opioids are common analgesics used to control pain in acute (*i.e.*, postoperative pain) and chronic conditions (*e.g.*, oncological pain, arthritis and headaches). Although they are not the first choice according to the World Health Organization analgesic ladder, it is still estimated that up to 90% of the population use them at least once in the lifetime while 0.56% are chronic users (greater than 6 mo assumption), especially elderly women[47]. The overall gastrointestinal effects consist in depression of the peristalsis with clinical manifestations of nausea, vomiting and constipation[48]. Opioids act on gut motility by decreasing the autonomic activity of the central nervous system and by binding to the mu- and kappa-receptors of the myenteric and submucosal plexuses in the gut[49,50]. The pathophysiological effects consist in an increase in the frequency of non-propulsive phasic contractions of the colon and decreased to absent propulsive migrating contractions[51]. The increase of non-propulsive contractions accounts for the higher intraluminal pressures. In fact, the administration of morphine produces high intraluminal sigmoid pressures in segments with colonic diverticula through the production of peristaltic segmentations[52-54]. These higher pressures may contribute either to the production of new diverticula or, in an already diseased segment, to

the perforation of some of them. On the other side the absence of propulsive complexes is responsible for the constipation and increased frequency of ileus. The reduction in the transit time may therefore prolong the exposure of the diverticular wall to potential pathogens[1].

Due to all these premises, the safety of administering opioids in patients with diverticular disease was questioned early in the medical literature[52]. However, the association between opioids and perforated diverticular disease is one of the least examined compared to the other classes of drugs. The first study that report the frequency of opioids use in patients with perforation from diverticular disease is based on a large cross-sectional study in the Norwich area (United Kingdom) that found opioids were used by 26% of the population presenting with diverticular perforation[2]. More recently, both case reports[55] and case-control studies[27,28] have further reported on the association among opioids and perforation from diverticular disease. In case-controls studies data were collectively presented for drugs used as required or regularly with no differentiation according to the duration or regularity of the assumption (Table 1)[27,28]. In the study of Piekarek *et al*[28], patients with diverticular disease were retrospectively examined and divided in two groups according to the perforation status. In the perforated group (case group) the use of opioids was present in 20.4% of patients (n = 11/54) while in the non-perforated group (control group) it was 6.0% (11/183). This corresponded to an OR for perforation with opioids of 4.5 (95%CI: 1.7-12.2). Differently from Piekarek *et al*[28], Humes *et al*[27] conducted a larger population-based study gathering data from the General Practice Research Database. In their study controls were healthy people not affected by the diverticular disease. Current opioids use was present in 6.3% (57/899) of perforated cases (case group) *vs* 2.4% (218/8980) of healthy patients (control group) with a lower OR than that reported by Piekarek *et al*[28] (2.2, 95%CI: 1.6-3.0)[27]. Both studies confirm that the current use of opioids increases the possibility of diverticular perforation. The different ORs observed can have different explanations. First, it is possible that differences not reported in the regularity or duration of opioids have significant influences on the occurrence of perforation. Second, the different control groups (healthy controls *vs* non-perforated diverticular disease) may provide a different baseline level for the calculation of the added risk towards perforation derived from the use of opioids, similar for the data reported on NSAIDs.

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers are a common class of drugs frequently prescribed in elderly people to treat hypertension and ischemic heart disease. They act by blocking the calcium channels in smooth muscle cells and therefore relaxing the contraction of non-voluntary musculature. Although this effect is desirable on peripheral circulation, to an extent it influences also the gastrointestinal motility and has been used to treat pathologic contractions of the gastrointestinal tract (*i.e.,* anal fissures from increased anal sphincter tone). The muscle-relaxant properties of these medications could have a beneficial effects in reducing intracolonic luminal pressures[56]. At the same time, some of them also increase the mucosal vascular flow therefore acting on the second main risk factor for diverticular perforation (weakened mucosal barrier)[57,58].

So far, three case control studies have analyzed the effects of Calcium channel blockers on the likelihood of perforation from diverticular disease (Table 1)[3,27,28]. In all studies the use of such medications was more frequent in controls than in patients that experienced perforated diverticular disease: 15% (72/150) in healthy controls *vs* 6.7% (8/120) in perforated patients for Morris *et al*[3], 1.2% (104/8980) in healthy controls *vs* 0.7% (6/899) in perforated patients for Humes *et al*[27], and 11.5% (21/183) in patients with simple diverticular disease *vs* 3.7% (2/54) in perforated patients according to[28]. These data corresponded to ORs of 0.4 (95%CI: 0.2-0.9)[3], 0.54 (95%CI: 0.24-1.24)[27], 0.14 (95%CI: 0.02-0.95)[28]. Among the three reports the only one in which the association was not statistically significant was the one of Humes *et al*[27] although the authors still suggested "a potentially protective role". The differences among this study (large population-based) and the others have already been outlined.

OTHER DRUGS

Few other classes of drugs have been sporadically investigated. Antimuscarinic drugs are commonly prescribed for depression, psychoses, but also as muscle relaxants for overactive bladder. Their characteristics could also influence the gastrointestinal musculature and prevent excessive contractions and therefore perforations from diverticular disease. However, the only study that compared healthy controls *vs* patients with perforated diverticular disease failed to provide a significant association[3]. Statins also were investigated in one study[27] for their potential anti-inflammatory qualities that could protect the diverticular mucosa[59]. Current use of a statin was associated with a lower risk of perforation (OR = 0.44, 95%CI: 0.20-0.95)[27].

CONCLUSION

Numerous drugs, largely used in the wards or at home, have an influence on patients with untreated diverticular disease. The consequences elicited can be disastrous, would ideally require an emergency operation with post-operative intensive care monitoring for definitive treatment, and influence the overall length of stay and final outcomes. Bearing these considerations in mind, the routine or chronic administration of pain-killers, steroids and non-steroidal anti-inflammatory should be balanced in patients with known diverticular disease as it normally happens with other associated conditions that could be affected by these drugs (*i.e.*, peptic ulcer disease or chron-

ic obstructive pulmonary disease). This is even more important in old and frail patients in which an eventual surgical treatment may not always be a possibility.

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