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

Gianpiero Gravante, Shuker Yahia

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.

© 2013 Baishideng. All rights reserved.

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.

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[3]. 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. 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. 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.

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 that present with diarrhoea, anaemia and non specific abdominal pain. Endoscopy revealed flat ulcers in the entire colon similar to ulcerations and erosions found in the small bowel. The median time from onset of symptoms to diagnosis was 1.8 years (range, 0.0-11.5 years) and prolonged use of NSAIDs increased the risk of mucosal damage more than the short use. In portions of large bowel not affected by underlying diseases numerous cases of strictures were also reported. Such lesions appeared on endoscopy as concentric “diaphragm-like” strictures similarly to those described in the small bowel. Finally, NSAIDs-induced perforations have been described especially in the cecum, usually caused by more distal strictures.

NSAIDs are frequently used to treat concomitant arthritic or cardiovascular diseases and not necessarily prescribed to alleviate symptoms in patients with diverticulitis. Most patients are even unaware of the presence of diverticular disease until the perforation occurred. In segments of the colon affected by diverticulitis NSAIDs increased the risk of bleeding 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). The incidence of NSAIDs in patients with perforated diverticular disease was compared with healthy controls or with patients having simple non-perforated diverticular disease. Overall, NSAIDs were present in 10% of patients with perforated diverticular disease (118/1182) and 3.8% of controls (391/10385). When compared with healthy controls, OR for the use of NSAIDs in patients with perforations was 1.8 (95% CI: 1.0-3.4) for Humes et al, 1.9 (95% CI: 0.96-3.4) for Mpfou et al, 2.1 (95% CI: 1.3-3.4) for Goh et al. When compared to simple diverticular disease OR were higher: 3.6 (95% CI: 1.5-8.4) for Pickarek et al, and 4.6 (95% CI: 1.7-12.5) for Goh et al. ORs results are consistent among studies and indicate a higher presence of NSAIDs in patients experiencing perforation compared to both control groups.

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%). Arthropathies are most likely to require a chronic treatment compared to the other indications.

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. At the same time, patients with chronic rheumatic conditions experienced a six-fold increase of death from complicated diverticular disease than the general population. The long-term use of corticosteroids has been described in chronic rheumatic patients suffering from perforated diverticular disease. Sporadic cases of diverticular perforation have also been reported in patients following neurosurgery operations, transplants or under steroid treatment for asthma and cancer. In some patients the diverticular disease was even unsuspected until the fatal entry happened.
the cyclo-oxygenase enzyme in the gut that normally produces prostaglandins with local protective effects\textsuperscript{[41]}. Prostaglandins enhance the gut mucosal barrier by stimulating the secretion of mucus and bicarbonate and increasing the local blood flow\textsuperscript{[42]}. Their absence predisposes the mucosa to the effects of noxious agents such as bacteria and toxins\textsuperscript{[43]}. 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\textsuperscript{[44]}. Four case-controls studies have investigated so far the association of perforated diverticular disease and corticosteroids (Table 1)\textsuperscript{[25-28]}. In two studies controls were healthy people\textsuperscript{[27,28]} and in the rest non-perforated diverticular disease\textsuperscript{[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 \textit{et al}\textsuperscript{[27]} , 13.2 (RR, 95\%CI: 1.81-96.5) for Corder\textsuperscript{[28]}, 28.3 (OR, 4.8-165.7) for Piekarek \textit{et al}\textsuperscript{[26]}, and 31.9 (OR, 95\%CI: 6.4-159.2) for Mpofu \textit{et al}\textsuperscript{[25]}. However, a more careful analysis shows that the risk increase presented by Humes \textit{et al}\textsuperscript{[27]} is markedly lower than those reported by the other authors\textsuperscript{[25-28]}. 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 \textit{et al}\textsuperscript{[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\%\textsuperscript{[25,28]}). This could explain the lower increase in the risk conferred by corticosteroids reported by Humes \textit{et al}\textsuperscript{[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 their lifetime while 0.56\% are chronic users (greater than 6 month assumption), especially elderly women\textsuperscript{[45]}. The overall gastrointestinal effects consist in depression of the peristalsis with clinical manifestations of nausea, vomiting and constipation\textsuperscript{[46]}. 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\textsuperscript{[47,48]}. 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\textsuperscript{[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\textsuperscript{[52-54]}. These higher pressures may contribute either to the production of new diverticula or, in an already diseased segment, to

| Author          | Country     | Drugs         | Patients (n) | Control group (n) | OR        |
|-----------------|-------------|---------------|--------------|-------------------|-----------|
| Gehl \textit{et al}\textsuperscript{[26]} | 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 \textit{et al}\textsuperscript{[25]} | United Kingdom | NSAIDs       | 64           | HC (320)           | 1.8 (95\%CI: 1.0-3.4) |
| Corder \textit{et al}\textsuperscript{[28]} | United Kingdom | NSAIDs       | -            | DD                 | 4.8 (95\%CI: 1.6-14.8) |
| Humes \textit{et al}\textsuperscript{[27]} | United Kingdom | NSAIDs       | 899          | HC (8980)          | 1.3 (95\%CI: 1.0-2.2) |
| Piekarek \textit{et al}\textsuperscript{[26]} | Sweden       | NSAIDs       | 54           | DD (183)           | 3.6 (95\%CI: 1.5-8.4) |
| Mpofu \textit{et al}\textsuperscript{[25]} | United Kingdom | Steroids     | 64           | HC (320)           | 31.9 (95\%CI: 6.4-159.2) |
| Corder \textit{et al}\textsuperscript{[28]} | United Kingdom | Steroids     | -            | DD                 | 3.2 (95\%CI: 1.8-6.5) |
| Humes \textit{et al}\textsuperscript{[27]} | United Kingdom | Steroids     | 899          | HC (8980)          | 2.7 (95\%CI: 1.4-6.6) |
| Piekarek \textit{et al}\textsuperscript{[26]} | Sweden       | Steroids     | 54           | DD (183)           | 28.3 (95\%CI: 4.8-165.7) |
| Humes \textit{et al}\textsuperscript{[27]} | United Kingdom | Opioids      | 899          | HC (8980)          | 2.2 (95\%CI: 1.6-3.0) |
| Piekarek \textit{et al}\textsuperscript{[26]} | Sweden       | Opioids      | 54           | DD (183)           | 4.5 (95\%CI: 1.7-12.2) |
| Morris \textit{et al}\textsuperscript{[26]} | United Kingdom | Ca\textsuperscript{+} | 120         | HC (480)           | 0.4 (95\%CI: 0.2-0.9) |
| Humes \textit{et al}\textsuperscript{[27]} | United Kingdom | Ca\textsuperscript{+} | 899         | HC (8980)          | 0.54 (95\%CI: 0.2-1.24) |
| Piekarek \textit{et al}\textsuperscript{[26]} | Sweden       | Ca\textsuperscript{+} | 54          | DD (183)           | 0.14 (95\%CI: 0.02-0.95) |

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

Due to all these premises, the safety of administering opioids in patients with diverticular disease was questioned early in the medical literature. 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 reported 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. More recently, both case reports and case-control studies 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). In the study of Pickarek et al., 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 (4.5% (95%CI: 1.7-12.2). Differently from Pickarek et al., Humes et al. 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% (57/989) of perforated cases (case group) vs 2.4% (218/8980) of healthy patients (control group) with a lower OR than that reported by Pickarek et al. (2.2, 95%CI: 1.6-3.0). 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. 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).

So far, three case control studies have analyzed the effects of Calcium channel blockers on the likelihood of perforation from diverticular disease (Table 1). In all studies the use of such medications was more frequent in controls than in patients that experienced perforated diverticular disease: 15% (72/470) in healthy controls vs 6.7% (8/120) in perforated patients for Morris et al., 1.2% (104/8980) in healthy controls vs 0.7% (6/899) in perforated patients for Humes et al., and 11.5% (21/183) in patients with simple diverticular disease vs 3.7% (2/54) in perforated patients according to Morris. These data corresponded to ORs of 0.4 (95%CI: 0.2-0.9), 0.54 (95%CI: 0.24-1.24), 0.14 (95%CI: 0.02-0.95). Among the three reports the only one in which the association was not statistically significant was the one of Humes et al. 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. Statins also were investigated in one study for their potential anti-inflammatory qualities that could protect the diverticular mucosa. Current use of a statin was associated with a lower risk of perforation (OR = 0.44, 95%CI: 0.20-0.95).

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.

REFERENCES

1. Morris CR, Harvey IM, Stebbings WS, Speakman CT, Kennedy HJ, Hart AR. Epidemiology of perforated colonic diverticular disease. Postgrad Med 2002; 78: 654-658 [PMID: 12496319 DOI: 10.1136/pmj.78.925.654]

2. Hart AR, Kennedy HJ, Stebbings WS, Day NE. How frequently do large bowel diverticula perforate? An incidence and cross-sectional study. Eur J Gastroenterol Hepatol 2000; 12: 661-665 [PMID: 10912487 DOI: 10.1097/00042737-200012 060-00016]

3. Morris CR, Harvey IM, Stebbings WS, Speakman CT, Kennedy HJ, Hart AR. Do calcium channel blockers and antimuscarinics protect against perforated colonic diverticular disease? A case control study. Gut 2003; 52: 1734-1737 [PMID: 14639592 DOI: 10.1136/gut.52.12.1734]

4. Wilcox CM, Cryer B, Triadafilopoulos G. Patterns of use and public perception of over-the-counter pain relievers: focus on nonsteroidal antiinflammatory drugs. J Rheumatol 2005; 32: 2218-2224 [PMID: 16265706]

5. Hawkey CJ, Lo Casto M. Inhibition of prostaglandin synthetase in human rectal mucosa. Gut 1983; 24: 213-217 [PMID: 6130107 DOI: 10.1136/gut.24.3.213]

6. Vane JR. Introduction: mechanism of action of NSAIDs. Br J Rheumatol 1996; 35 Suppl 1: 1-3 [PMID: 8630629 DOI: 10.1093/rheumatology/35.suppl.1]

7. Shibuya T, Ohkusa T, Yokoyama T, Harada A, Beppu K, Sakamoto N, Osada T, Nagahara A, Terai T, Otaka M, Oghara T, Watanabe S. Colonic mucosal lesions associated with long-term or short-term administration of nonsteroidal anti-inflammation drugs. Colorectal Dis 2010; 12: 1113-1121 [PMID: 19817771 DOI: 10.1111/j.1463-1318.2009.01948.x]

8. Puspok A, Kiener HP, Oberhuber G. Clinical, endoscopic, and histologic spectrum of nonsteroidal anti-inflammatory drug-induced lesions in the colon. Dis Colon Rectum 2000; 43: 685-691 [PMID: 10826432 DOI: 10.1007/BF02255899]

9. Higuchi K, Umegaki E, Watanabe T, Yoda Y, Morita E, Murano M, Tokioka S, Arakawa T. Present status and strategy of NSAIDs-induced small bowel injury. J Gastroenterol 2009; 44: 879-888 [PMID: 19568887 DOI: 10.1007/s00535-009-0102-2]

10. Robinson MH, Wheatley T, Leach IH. Nonsteroidal anti-inflammatory drug-induced colonic strictures. An unusual cause of large bowel obstruction and perforation. Dig Dis Sci 1995; 40: 315-319 [PMID: 7851196 DOI: 10.1007/BF02065416]

11. Aloysius MM, Kaye PV, Lobo DN. Non-steroidal anti-inflammatory drug (NSAID)-induced colonic strictures and perforation: a case report. Dig Liver Dis 2006; 38: 276-278 [PMID: 16203193 DOI: 10.1016/j.dld.2005.09.003]

12. Penner RM, Williams CN. Resolution of multiple severe nonsteroidal anti-inflammatory drug-induced colonic strictures with prednisone therapy: a case report and review of the literature. Can J Gastroenterol 2003; 17: 497-500 [PMID: 12945011]

13. Ribeiro A, Wolfsen HC, Wolfe JT, Loeb DS. Colonic strictures induced by nonsteroidal anti-inflammatory drugs. South Med J 1998; 91: 568-572 [PMID: 9634121 DOI: 10.1097/00007619-199806000-00012]

14. Gargoti D, Chauvassade S, d’Alterecho L, Desbaizelle F, Grandjouan S, Louvel A, Douvin J, Caussé X, Festin D, Chapuis P. Nonsteroidal anti-inflammatory drug-induced colonic strictures: two cases and literature review. Am J Gastroenterol 1995; 90: 2035-2038 [PMID: 7485018]

15. Huber T, Ruchti C, Halter F. Nonsteroidal antiinflammatory drug-induced colonic strictures: a case report. Gastroenterol-
of 1666 patients with rheumatoid arthritis who have died. J Rheumatol 1995; 22: 2214-2217 [PMID: 8835551]

32 Myllýkangas-Luosujärvi R. Diverticularis--a primary cause of life-threatening complications in rheumatoid arthritis. Clin Exp Rheumatol 1995; 13: 79-82 [PMID: 7774108]

33 Durieux S, Rosenberg S, Bourgeois P. Complications of colonic diverticular disease during rheumatoid polyarthritis: 7 cases. Rev Med Int Enn 1999; 20: 50-53 [PMID: 10228019]

34 Bowman S, Paice E, Binder A. Death from unsuspected diverticular disease in patients taking corticosteroids for polymyalgia rheumatica or giant cell arteritis. Br J Rheumatol 1991; 30: 159-160 [PMID: 2012956 DO: 10.1093/ rheumatology/30.2.159-a]

35 Hutchinson D, Lynch M. Sigmoid diverticular abscess perforation in 2 patients with rheumatoid arthritis treated with high dose corticosteroids. A cautionary tale. J Rheumatol 2001; 28: 1935-1936 [PMID: 11508608]

36 Candelas G, Jover JA, Fernandez B, Rodriguez-Olaverri JC, Calatayud J. Perforation of the sigmoid colon in a rheumatoid arthritis patient treated with methylprednisolone pulses. Scan J Rheumatol 1998; 27: 152-153 [PMID: 9572644 DOI: 10.1080/0300974984410506]

37 Oehler U, Bulatko A, Jens H, Helpap B. Lethal complications in a case of sigmoid diverticulitis. A case report. Gen Diagn Pathol 1997; 142: 231-234 [PMID: 9065589]

38 Weiner HL, Rezai AR, Cooper PR. Sigmoid diverticular perforation in neurosurgical patients receiving high-dose corticosteroids. Neurosurgery 1993; 33: 40-43 [PMID: 855846 DOI: 10.1227/00006123-199307000-00006]

39 Weaver TM, Fullerton DA, Zamora MR, Badesch DB, Weill D, Brown JM, Campbell DN, Grover FL. Colon perforation after lung transplantation. Ann Thorac Surg 1996; 62: 839-843 [PMID: 8784016 DOI: 10.1016/S0003-4975(96)00393-1]

40 Carson SD, Krom RA, Uchida K, Yokota K, West JC, Weil R. Colon perforation after kidney transplantation. Ann Surg 1978; 188: 109-113 [PMID: 552278 DOI: 10.1097/00000658-197807000-00018]

41 Dalla Valle R, Capocasale E, Mazzoni MP, Busi N, Benozzi L, Sivelli R, Sianesi M. Acute diverticulitis with colon perforation in renal transplantation. Transplant Proc 2005; 37: 2507-2510 [PMID: 16182727 DOI: 10.1016/j.transproceed.2005.06.059]

42 Sawyer OI, Garvin P, Codd JE, Graff RJ, Newton WT, Willman VL. Colorectal complications of renal allograft transplantation. Arch Surg 1978; 113: 84-86 [PMID: 339877 DOI: 10.1001/archsurg.1978.01370130086016]

43 Soravia C, Baldi A, Kartheuser A, Mourad M, Kestens P, Detry R, Sguiffet JP. Acute colonic complications after kidney transplantation. Acta Chir Belg 1995; 95: 157-161 [PMID: 7610750]

44 Munsch B, Chaufert B, Cuny C, Lorcerie B, Martin F. Perforation of colonic diverticulum under corticoids: a complication to be known and recognized. Rev Med Interne 1995; 16: 137-140 [PMID: 7709103]

45 Davies NM. Toxicity of nonsteroidal anti-inflammatory drugs in the large intestine. Dis Colon Rectum 1995; 38: 1311-1321 [PMID: 7497845 DOI: 10.1007/BF02049158]

46 Cappell MS, Marks M. Acute colonic diverticular perforation presenting as left ear pain and facial swelling due to cervical subcutaneous emphysema in a patient administered corticosteroids. Ann J Gastroenterol 1992; 87: 899-902 [PMID: 1615948]

47 Cicero TJ, Wong G, Tian Y, Linsky M, Todorov A, Isenberg K. Co-morbidity and utilization of medical services by pain patients receiving opioid medications: data from an insurance claims database. Pain 2009; 144: 20-27 [PMID: 19362417 DOI: 10.1016/j.pain.2009.01.026]

48 Brock C, Olesen SS, Olesen AE, Frøkjaer JB, Andreasen T, Drewes AM. Opioid-induced bowel dysfunction: physopathology and management. Drugs 2012; 72: 1847-1865 [PMID: 22905533 DOI: 10.2165/11634970-000000000-00000]

49 Galligan JD, Burks TF. Centrally mediated inhibition of small intestinal transit and motility by morphine in the rat. J Pharmacol Exp Ther 1983; 226: 356-361 [PMID: 6875849]

50 Shahbazian A, Heinemann A, Schmidhammer H, Beubler E, Holzer-Petsch U, Holzer P. Involvement of mu- and kappa-, but not delta-, opioid receptors in the peristaltic motor depression caused by endogenous and exogenous opioids in the guinea-pig intestine. Br J Pharmacol 2002; 135: 741-750 [PMID: 11854622 DOI: 10.1038/sj.bjp.0704527]

51 Ferraz AA, Cowles VE, Condron RE, Schulte WJ. Opioid and nonopioid analgesic drug effects on colon contractions in monkeys. Dig Dis Sci 1995; 40: 1417-1419 [PMID: 7628261 DOI: 10.1007/BF02285185]

52 Painter NS, Truelove SC. Potential dangers of morphine in acute diverticulitis of the colon. Br Med J 1963; 2: 33-34 [PMID: 13941128 DOI: 10.1136/bmj.2.5348.33]

53 Painter NS, Truelove SC. The intraluminal pressure patterns in diverticulosis of the colon. I. Resting patterns of pressure. II. The effect of morphine. Gut 1964; 5: 201-213 [PMID: 14178701 DOI: 10.1136/gut.5.3.201]

54 Painter NS, Truelove SC, Ardran GM, Tuckey M. Effect of morphine, progistine, pethidine, and probanthine on the human colon in diverticulosis studied by intraluminal pressure recording and cineradiography. Gut 1965; 6: 57-63 [PMID: 14259424 DOI: 10.1136/gut.6.1.57]

55 Soliani G, Dominici M, Bergossi L, Basaglia E, Pauli S, Carcoforo P. Acute colon diverticulitis in multiple myeloma patient: an unusual presentation of a colonic perforation. Case report. Ann Ital Chir 2002; 73: 643-646 [PMID: 12820590]

56 Bassotti G, Calcarca C, Annese V, Fiorella S, Roselli P, Morelli A. Nifedipine and verapamil inhibit the sigmoid colon myoelectric response to eating in healthy volunteers. Dis Colon Rectum 1998; 41: 377-380 [PMID: 9514436 DOI: 10.1007/ BF02237495]

57 Greenstein SM, Sun S, Kim DY, Schreiber TC, Schechner RS, Tellis VA. Nifedipine prevents tacrolimus-induced intestinal hemodynamic and functional impairments. Transplant Proc 1998; 30: 2668-2669 [PMID: 9745540 DOI: 10.1016/ S0004-1341(98)00781-7]

58 Sun S, Greenstein SM, Kim DY, Schreiber TC, Schechner RS, Tellis VA. Nifedipine protects small intestine from cyclosporine-induced hemodynamic and functional impairment. J Surg Res 1997; 69: 295-299 [PMID: 9224396 DOI: 10.1016/j.sjres.1997.5035]

59 Terblanche M, Almog Y, Rosenson RS, Smith TS, Hackam DG. Statins and sepsis: multiple modifications at multiple levels. Lancet Infect Dis 2007; 7: 358-368 [PMID: 17448939 DOI: 10.1016/S1473-5899(07)70111-1]
