REVIEW ARTICLE

Drug Safety 2000 Jan; 22 (1): 53-72
0114-5916/00/0001-0053/$20.00/0

Drug-Induced Diarrhoea

Olivier Chassany, Alessandra Michaux and *Jean François Bergmann*

Internal Medicine Department, Lariboisière University Hospital, Paris, France

Contents

Abstract

Diarrhoea is a relatively frequent adverse event, accounting for about 7% of all drug adverse effects. More than 700 drugs have been implicated in causing diarrhoea; those most frequently involved are antimicrobials, laxatives, magnesium-containing antacids, lactose- or sorbitol-containing products, nonsteroidal anti-inflammatory drugs, prostaglandins, colchicine, antineoplastics, antiarrhythmic drugs and cholinergic agents. Certain new drugs are likely to induce diarrhoea because of their pharmacodynamic properties; examples include anthraquinone-related agents, α-glucosidase inhibitors, lipase inhibitors and cholinesterase inhibitors. Antimicrobials are responsible for 25% of drug-induced diarrhoea. The

disease spectrum of antimicrobial-associated diarrhoea ranges from benign diarrhoea to pseudomembranous colitis.

Several pathophysiological mechanisms are involved in drug-induced diarrhoea: osmotic diarrhoea, secretory diarrhoea, shortened transit time, exudative diarrhoea and protein-losing enteropathy, and malabsorption or maldigestion of fat and carbohydrates. Often 2 or more mechanisms are present simultaneously.

In clinical practice, 2 major types of diarrhoea are seen: acute diarrhoea, which usually appears during the first few days of treatment, and chronic diarrhoea, lasting more than 3 or 4 weeks and which can appear a long time after the start of drug therapy. Both can be severe and poorly tolerated.

In a patient presenting with diarrhoea, the medical history is very important, especially the drug history, as it can suggest a diagnosis of drug-induced diarrhoea and thereby avoid multiple diagnostic tests. The clinical examination should cover severity criteria such as fever, rectal emission of blood and mucus, dehydration and bodyweight loss. Establishing a relationship between drug consumption and diarrhoea or colitis can be difficult when the time elapsed between the start of the drug and the onset of symptoms is long, sometimes up to several months or years.

Diarrhoea is a relatively frequent adverse event, accounting for about 7% of all drug adverse effects.[1-3] More than 700 drugs have been implicated in causing diarrhoea; those most frequently involved are antimicrobials, laxatives, magnesium-containing antacids, lactose- or sorbitol-containing products, nonsteroidal anti-inflammatory drugs (NSAIDs), prostaglandins, colchicine, antineoplastics, antiarrhythmic drugs and cholinergic agents.[4,5] The high frequency of drug-induced diarrhoea is not surprising, since the intestinal mucosa is the first absorption site of orally administered drugs.

The mechanism of drug-induced diarrhoea is often multifactorial and sometimes remains unclear.[6] Drug-induced diarrhoea is sometimes unrecognised or only diagnosed after a delay. This situation can be related to the fact that the patient stops the drug on his or her own initiative as soon as the diarrhoea appears, or that no association is made between the diarrhoea and the drugs taken. For example, the patient may not be asked about drug use, or does not remember or want to list all the drugs, or the drugs used by the patient are not known to induce diarrhoea.

1. Definition and Pathophysiology of Diarrhoea

Diarrhoea is defined by an increased frequency of bowel movements (≥3 per 24 hours), and/or decreased stool consistency, and/or increased stool weight (>200g per 24 hours).[4]

Several pathophysiological mechanisms of drug-induced diarrhoea have been described (fig. 1).[7] These include:

- ingestion of unusual amounts of poorly absorbed and osmotically active solutes such as mannitol, sorbitol, lactulose or magnesium salts contained in antacids or laxatives (osmotic diarrhoea)
- increased small intestinal ion secretion or inhibition of normal active ion absorption, leading to an excess of water and electrolytes in the intestinal lumen and in the stools (secretory diarrhoea)
- impairment of fluid absorption by activation of adenylate cyclase within the small intestinal enterocyte, which increases the level of cyclic AMP (e.g. bisacodyl, prostaglandins, chenodeoxycholic acid)
- inhibition of Na^+/K^+ ATPase (e.g. auranofin, colchicine, digoxin, olsalazine)

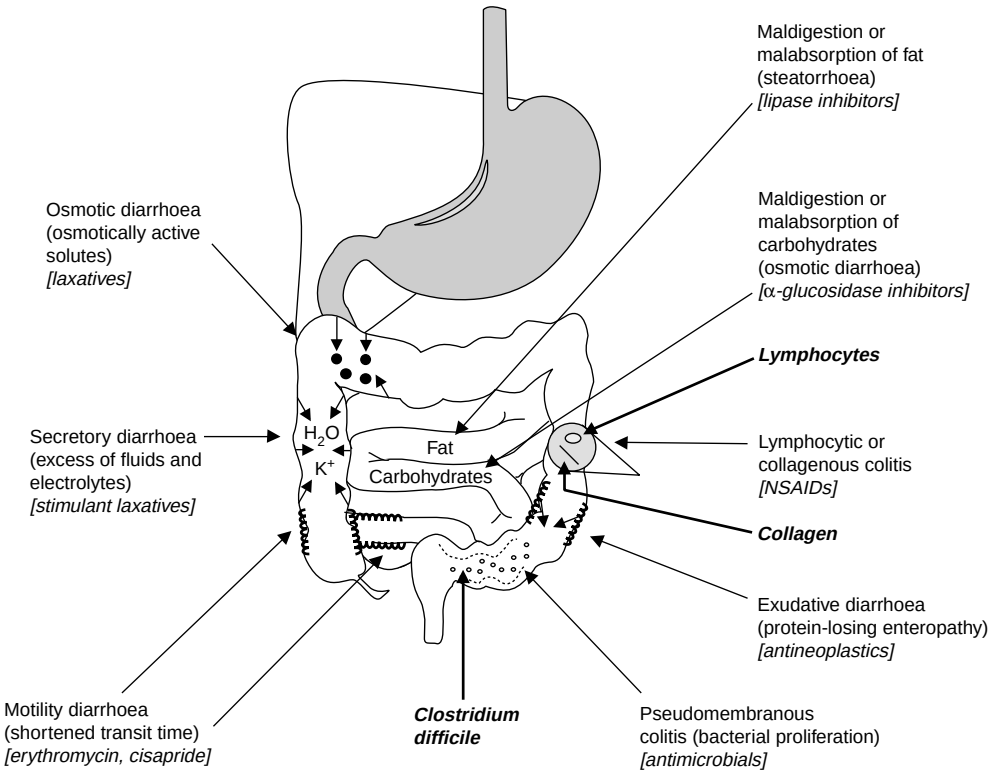

Fig. 1. Major pathophysiological mechanisms of drug-induced diarrhoea.

- disturbance of intestinal motility, i.e. shortened transit time (e.g. cisapride, erythromycin)
- exudation of blood, mucus and proteins into the bowel lumen because of disruption of the integrity of the intestinal mucosa through inflammatory and ulcerated lesions (exudative diarrhoea)
- malabsorption[8] or maldigestion of fat and carbohydrates, as with auranofin or α-glucosidase inhibitors.

Often 2 or more mechanisms are present simultaneously (table I).

In most cases of drug-induced diarrhoea there is no detectable organic lesion, except for pseudomembranous colitis secondary to antibacterials and rare observations of small intestinal enteropathy[6] and colitis.[3] Histological colitis, e.g. collagenous and lymphocytic colitis, has been recognised recently.[3] NSAIDs were the first drugs to be incriminated in the appearance of collagenous colitis.[9,10] Since then, many other compounds have been found to be involved in histological colitis, e.g. flavonoid-related veinotonic agents,[11] cimetidine,[12] ticlopidine,[13] and more recently the combination levodopa-benserazide,[14] a preparation containing ferrous sulfate,[15] carbamazepine[16] and simvastatin.[17] The clinical presentation of these types of colitis is a watery diarrhoea, sometimes severe, with no macroscopic abnormality during endoscopy. The mechanism of the diarrhoea may be related to a reduction of colonic fluid absorption.[18]

In clinical practice, 2 major types of diarrhoea are considered: acute diarrhoea, which usually appears during the first few days of treatment, and chronic diarrhoea, lasting more than 3 or 4 weeks and which can appear a long time after the start of

drug treatment. Both can be severe and poorly tolerated.

2. Agents Causing Drug-Induced Diarrhoea

2.1 Antibacterials

Antibacterial-associated diarrhoea is a common adverse reaction to most types of antibacterials, e.g. penicillins,[19] cephalosporins,[20] clindamycin[21] and also quinolones[22] and macrolides,[23] with a frequency up to 40% depending largely on the antibacterial spectrum of the drug. Antibacterials are responsible for 25% of drug-induced diarrhoea.[24] The disease spectrum of antibacterial-associated diarrhoea ranges from benign diarrhoea to pseudomembranous colitis. Most frequently, however, diarrhoea is benign, appearing during the first days of treatment, whatever the class of antibacterial, and resolving spontaneously after discontinuation of treatment.

2.1.1 Pathophysiology of Antibacterial-Associated Diarrhoea

The pathophysiology of antibacterial-associated diarrhoea is explained by disruption of the normal intestinal microflora, which can have 2 consequences: proliferation of pathogenic micro-organisms and impairment of the metabolic function of the microflora.[25,26] When an antibacterial changes the composition of the microflora by eliminating sensitive micro-organisms, this phenomenon is usually of no clinical significance, and the normal microflora is re-established shortly after therapy is stopped. In some patients, however, the modification of the normal microflora and the loss of normal colonisation resistance can induce proliferation of opportunistic pathogens such as *Clostridium difficile*, which is responsible for more than 20% of cases of antibacterial-associated diarrhoea and almost all cases of pseudomembranous colitis.[24,26] The pathogenesis of *C. difficile* is exerted by 2 toxins and is expressed as diarrhoea, colitis and pseudomembranous colitis. The decrease in the normal intestinal microflora can also result in impaired fermentation of poorly absorbed carbo-

Table I. Principal drugs implicated in the different pathophysiological mechanisms of diarrhoea

Osmotic
Lactulose, sorbitol, fructose and mannitol (laxatives and sugar-free products)
Magnesium (laxatives, antacids and sugar substitutes)
Secondary to maldigestion of carbohydrates
antibacterials (ampicillin)
acarbose (α-glucosidase inhibitor)
Secretory
Antibacterials (through a diminution of production of short-chain fatty acids)
Antineoplastics
Auranofin (gold salt)
Biguanides
Calcitonin
Cardiac glycosides
Chenodeoxycholic acid
Colchicine
Diacerein
Nonsteroidal anti-inflammatory drugs
Olsalazine
Prostaglandins (misoprostol)
Stimulant laxatives: ricinoleic acid, bisacodyl, oxyphenisatin, phenolphthalein, derivatives of anthraquinone
Ticlopidine
Motility
Cisapride (prokinetic)
Colchicine
Macrolides (erythromycin) and some other antibacterials
Thyroid hormones
Ticlopidine
Exudative (protein-losing enteropathy)
Antibacterials
Antineoplastics
Nonsteroidal anti-inflammatory drugs
Simvastatin
Stimulant laxatives
Ticlopidine
Malabsorption of fat (steatorrhoea)
Aminoglycosides (neomycin, kanamycin)
Auranofin
Biguanides
Cholestyramine
Colchicine
Laxatives
Methyldopa
Octreotide
Orlistat (lipase inhibitor)
Polymixin, bacitracin
Tetracyclines

Table I. Contd

Microbial proliferation and pseudomembranous colitis
Antibacterials
Antineoplastics
Immunosuppressive agents
Nonsteroidal anti-inflammatory drugs
Histological colitis
Collagenous colitis
Nonsteroidal anti-inflammatory drugs
Lymphocytic colitis
Carbamazepine
Cimetidine, ranitidine
Ferrous sulfate
Levodopa-benserazide
Simvastatin
Ticlopidine
Veinotonics
Vinburnine
Colitis, ileitis
Antibacterials (haemorrhagic colitis)
Antineoplastics
Auranofin
Cyclosporin
Nonsteroidal anti-inflammatory drugs
Perazine

hydrates, leading to osmotic diarrhoea[27] and/or to reduced production of short-chain fatty acids,[28] which reduces the colonic absorption of fluid and results in secretory diarrhoea. Thus, in antibacterial-associated diarrhoea, several mechanisms are generally implicated, depending on the molecule.[24,26]

2.1.2 Risk Factors

The effect of an antimicrobial agent on the intestinal ecosystem, and thus the frequency of diarrhoea, depends largely on its antibacterial spectrum and its concentration in the intestinal lumen.[25,26,29] Antimicrobial agents with the broadest spectrum, especially against Enterobacteriaceae and anaerobic bacteria (e.g. aminopenicillins, cephalosporins and clindamycin),[30] and those with a high intraluminal concentration in the intestinal tract (e.g. antibacterials poorly or incompletely absorbed or secreted into the bile) lead to greater modifications of the commensal flora. For example, the administration of ceftriaxone, a third generation cephalosporin which is mainly eliminated by biliary secretion, is associated with a 10 to 40% frequency of antibacterial-associated diarrhoea.[31,32] The incidence of gastrointestinal adverse effects with amoxicillin-clavulanic acid is greater than that with amoxicillin alone.[19] The other risk factors for antibacterial-associated diarrhoea are the duration of antibacterial therapy, repeated antibacterial therapy, and the combination of antibacterials. The dosage of antibacterial and the route of administration are not risk factors.[26]

2.1.3 Pseudomembranous Colitis

Pseudomembranous colitis is rare but severe.[33] The mechanism is the emergence and proliferation of *C. difficile*,[33] which secretes 2 toxins: enterotoxin A and cytotoxin B. Enterotoxin A fixes on to the brush-border membrane of enterocytes and induces lesions and an inflammatory response. Cytotoxin B may also cause mucosal damage in humans.[34] Antibacterials that reach high concentrations in the intestinal lumen and are active against bowel flora are more likely to promote overgrowth of *C. difficile*.[33] Aminopenicillins are responsible in 35% of cases,[19,35-37] cephalosporins in 30%,[31,32,38] and lincosamides (clindamycin) in 15%.[30,39]

Symptoms generally appear 5 to 10 days after the start of therapy, but shorter periods and longer delays up to 1 month are possible. The acute colitis can be severe with profuse diarrhoea (rarely with blood), abdominal pain and bloating, fever and a frank altered general status. Endoscopy reveals raised white to yellow plaques covering a normal colonic mucosa or moderately erythematous mucosa. The pseudomembranes can spread throughout the colon, occasionally sparing the rectum. At histological examination, the membranes consist of fragments of fibrin, leucocytes and epithelial cells, and adhere to the intestinal mucosa, which is superficially damaged. Stool culture for *C. difficile* and/or the isolation of toxins are positive in 70 to 95% of patients.[40,41]

Mortality in a community-based series of patients hospitalised with *C. difficile* colitis reached 3%.[42] Mortality is due to local complications (e.g. toxic megacolon, haemorrhage, perforation) or

general complications (e.g. dehydration, shock, sepsis).

Other antimicrobial agents occasionally involved in the occurrence of pseudomembranous colitis include aminoglycosides, tetracyclines, macrolides,[23,43] sulphonamides, chloramphenicol, imidazoles and quinolones.[22] The increasing number of patients being diagnosed with *Helicobacter pylori* infection and treated with amoxicillin and other antibacterials may increase the incidence of pseudomembranous colitis.[44]

2.1.4 Other Presentations of Antibacterial-Associated Diarrhoea

A haemorrhagic colitis, revealed by abdominal pain and profuse haemorrhagic diarrhoea, may rarely complicate treatment with an aminopenicillin[45-47] or other antibacterials.[48-50] Endoscopy shows a diffuse haemorrhagic mucosa.[51] The histological aspect is different from that of ischaemic colitis, only the superficial layer of the mucosa being infiltrated by blood, without necrosis. The pathogenesis is the same as for pseudomembranous colitis. Involvement of *C. difficile* has been suggested but not confirmed. Other pathogens such as *Klebsiella oxytoca*,[51-53] *Staphylococcus aureus*, *Candida albicans*,[54] *Proteus* spp., *Pseudomonas* spp. and *Clostridium perfringens* have been isolated.

A malabsorptive diarrhoea can occur after the long term use of oral antibacterials such as aminoglycosides (neomycin, kanamycin), polymixin and bacitracin.[8,55] The malabsorption results from 2 actions: the antibacterial damages the small intestinal mucosa, leading to villous atrophy of the intestinal epithelium and to a reduction of the enzyme activity of enterocytes; and the antibacterial in the intestinal lumen binds bile acids and thus reduces the absorption of fat.[8]

A secretory diarrhoea can occur with some antibacterials without microbial proliferation and without mucosal damage. In 15 to 30% of patients, clindamycin causes a watery diarrhoea[56] without colitis or the presence of *C. difficile*.[21]

Diarrhoea due to disturbed motility has been described with oral and parenteral administration of some macrolides, especially erythromycin,[57] and less with penicillins, cephalosporins, tetracyclines, sulphonamides and quinolones.[58] A dose-effect relationship exists for macrolides and β-lactam antibacterials, symptoms being worse the higher the dosage of antibacterial and the longer the duration of treatment. Symptoms can occur after the very first administration of the antibacterial, and can be controlled by taking the antibacterial with a meal. This has been studied particularly with erythromycin, intravenous administration of which, especially in large doses, may cause diarrhoea, nausea, vomiting and abdominal cramps. The mechanism could be related to the fact that erythromycin acts as a motilin receptor agonist to stimulate gastrointestinal motility[57] and to shorten orocaecal transit time.[59] 10% of patients presenting with a motor diarrhoea show increased small intestinal motility, with an increased length and intensity of the migrating motor complexes of phase III.[57,60]

2.2 Nonsteroidal Anti-Inflammatory Drugs

The recognition of lower gastrointestinal tract adverse reactions to NSAIDs is recent and probably underestimated.[61,62] Diarrhoea is not infrequent, occurring, for example, in 3 to 9% of patients treated with flurbiprofen, mefenamic acid, naproxen, niflumic acid, diclofenac, sulindac or nabumetone.[63] Although the mechanisms of diarrhoea remain unclear, it is established that NSAIDs, including aspirin (acetylsalicylic acid), reduce the activity of cyclo-oxygenase, thus reducing the synthesis of prostaglandins and increasing the synthesis of leukotrienes by the intestinal mucosa. This results in a reduction of the blood flow in the intestinal mucosa and an increase in intestinal permeability, which can promote the penetration of bacteria and toxins.[64,65] The clinical spectrum of diarrhoea varies from acute benign diarrhoea to severe colitis. Several observations of pseudomembranous colitis following diclofenac prescription[66] have been reported, presenting as an acute diarrhoea with blood and mucus and with positive culture of *C. difficile* in the stool.[67]

Other severe reactions such as acute enteritis,[68] protein-losing enteropathy,[69] colitis and/or proctitis can occur *de novo* during NSAID use, mostly with mefenamic acid, but also with ibuprofen, naproxen, piroxicam, diclofenac and flufenamic acid.[70,71] The presentation is an acute diarrhoea with >10 stools per day, usually with mucus and blood and with bodyweight loss.[70] Endoscopic examination can show erythematous, ulcerated and haemorrhagic colonic mucosa.[71-73] Most of the observations reported tended to be in elderly patients treated over several months with NSAIDs. Although recovery is rapid when the NSAID is withdrawn, complications such as perforations or lower intestinal haemorrhage can be life-threatening.[74] A positive rechallenge with NSAIDs has been reported in 12 patients.[71] In patients with a history of lower bowel disease, e.g. ulcerative colitis, ischaemic colitis or perforation of sigmoid diverticula, NSAIDs such as indomethacin, naproxen, piroxicam and aspirin are likely to reactivate or complicate the disease.[75-81] Finally, NSAIDs have been associated with collagenous colitis,[9,10,82] occurring mostly after long term use (>6 months),[9] with 1 case of positive rechallenge.[9]

2.3 Drugs Affecting Cardiovascular Function

2.3.1 Ticlopidine

Apart from haematological adverse effects, ticlopidine can result in diarrhoea, mostly acute and benign, which resolves after withdrawal of the drug. Increased motility is thought to be the principal mechanism in acute diarrhoea.[83] Several observations of chronic and more severe diarrhoea with marked bodyweight loss, resolving rapidly when ticlopidine is stopped, have been reported.[84-87] The time elapsing between the start of drug treatment and the occurrence of diarrhoea can be very long, up to 2 years.[87]

The mechanism responsible for the diarrhoea is uncertain. When performed, colonoscopy does not reveal any macroscopic lesion. Histological examination of biopsy specimens can reveal an infiltrate of polymorphonuclear cells, mostly lymphocytes, but also neutrophils or eosinophils.[13,88,89] Subtle histopathological changes have been recently described in ticlopidine-induced microscopic colitis in 9 patients.[13] These lesions of lymphocytic colitis can also induce an exudative enteropathy.[90,91] Ticlopidine also increases the amount of prostaglandins in the intestinal mucosa. This could lead to a secretory diarrhoea due to increased transport of fluids and electrolytes from the intestinal cells to the lumen.

2.3.2 Quinidine

Gastrointestinal effects, including diarrhoea, occur in about 8 to 30% of patients receiving quinidine,[92,93] but only 10% of patients need to discontinue treatment.[93] The diarrhoea may be related to a local irritation, secondary to a high concentration of ions in the intestinal lumen, as quinidine exists in a strong acidic salt form. Diarrhoea can be controlled with aluminium hydroxide gel or cholestyramine without interfering with the antiarrhythmic efficacy of quinidine.[94,95] Food may also alleviate this diarrhoea.[93]

2.3.3 Antihypertensive Drugs

Propranolol, a β-blocker, is also responsible for inducing diarrhoea which may be severe enough to require withdrawal of the drug.[96,97] More rarely, observations of diarrhoea induced by calcium antagonists have been reported.[98,99] A few cases of colitis with bloody diarrhoea have been reported in patients treated with methyldopa.[100,101] In 3 cases, the rechallenge was positive.[102] One observation of severe malabsorption associated with protein-losing enteropathy and positive rechallenge has also been published.[103]

2.3.4 Cardiac Glycosides

Symptoms such as diarrhoea, nausea, vomiting, abdominal pain and anorexia are early signs of digoxin toxicity and overdose.[104-106]

2.3.5 Veinotonic Agents

Cyclo 3 Fort® is a flavonoid-related veinotonic drug used in France. There have been several reports of chronic diarrhoea with this agent, usually appearing after long term (several weeks or months) use.[107,108] The diarrhoea was usually se-

vere with or without blood and mucus. Most cases were poorly tolerated, with bodyweight loss and hypokalaemia. The drug-induced diarrhoea was diagnosed after a delay of up to 5 months, after long and negative diagnostic procedures.[108] Endoscopy showed no macroscopic lesions. Histological findings were consistent with lymphocytic colitis, with an epithelial infiltrate of lymphocytes and plasmocytes.[108-110] Beaugerie et al.[11] concluded that lymphocytic colitis may be secondary to chronic activation of the mucosal immune system by one or several components of the drug. Diarrhoea ceased after withdrawal of the drug, and colitis disappeared within a few months. In several cases, clinical and histological positive rechallenge firmly demonstrated the involvement of the drug.[11] The possibility of a positive clinical rechallenge without histological relapse could suggest that diarrhoea and lymphocytic colitis are 2 independent consequences of flavonoid intake.

Other veinotonic agents licensed in France have been associated with chronic diarrhoea.[111-113] Similarly, a drug containing saponin, administered for venous insufficiency, led to watery diarrhoea with a positive rechallenge.[114]

2.4 Agents for Control of Gastric Acidity and Gastro-Oesophageal Reflux

2.4.1 Histamine H_2 Receptor Antagonists

The frequency of drug-induced diarrhoea is as low as 2% with antiulcer drugs.[115,116] The clinical presentation is benign diarrhoea responding to withdrawal of the drug. Recently, there have been several reports of chronic diarrhoea occurring during ranitidine treatment[117] and associated with histological abnormalities, such as lymphocytic colitis and cellular apoptosis.[118] The chronic diarrhoea appeared within several weeks or months after the start of treatment and resolved within 48 hours of discontinuation of ranitidine. Histological features took up to 6 months to disappear. A case of watery diarrhoea after starting cimetidine treatment was also detailed. Macroscopically, sigmoidoscopy and colonoscopy were normal. Histology revealed features consistent with collagenous colitis.[119] A rechallenge was positive in a patient presenting with 10 to 20 stools per day during cimetidine therapy.[120] The mechanism of this diarrhoea remains unclear.

So far, diarrhoea induced by proton pump inhibitors is rare (about 4%) and benign.[121] No histology studies have yet been reported.

2.4.2 Prostaglandins

Misoprostol is a prostaglandin E_1 analogue with gastric antisecretory and cytoprotective properties. It is known to interfere with the intestinal transport of fluids and electrolytes.[122] Prescribed at a dosage of 800 μg/day, misoprostol induced diarrhoea among 14 to 40% of patients.[123-125] Such diarrhoea is mostly benign and well tolerated, but can necessitate dosage reduction to 400 μg/day or withdrawal of misoprostol, thus altering the preventive efficacy of the drug, as misoprostol has been proved efficient in the prevention of NSAID-induced ulceration at the dosage of 800 μg/day.[123] In 1 clinical trial, the frequency of diarrhoea was still higher with misoprostol 600 μg/day than with placebo.[126] With a combination of diclofenac 50mg and misoprostol 200μg twice or 3 times daily, diarrhoea occurred in 20% of patients compared with 11% of patients receiving diclofenac alone.[127] In comparison with ibuprofen, piroxicam and naproxen used alone, a fixed dose combination of diclofenac-misoprostol caused a higher incidence of diarrhoea.[128,129] This adverse effect may be minimised by taking misoprostol after meals or at bedtime.

Dose-related diarrhoea is also reported with enprostil, a prostaglandin E_2 analogue used in the same indications as misoprostol.[130] A similar or greater incidence of diarrhoea is observed with prostaglandin E_2 (dinoprostone) and $F_{2\alpha}$ (dinoprost) prescribed to induce contraction of the uterus.[131]

2.4.3 Cisapride

The most common adverse event associated with cisapride, a prokinetic used to relieve the symptoms of gastro-oesophageal reflux, is diarrhoea reported by about 10% of patients.[132,133] Diarrhoea and other gastrointestinal adverse effects

(e.g. abdominal pain, constipation, flatulence) seem to be dose-related, as cisapride 20 mg/day is less well tolerated than 10 mg/day. These adverse effects are explained by the fact that cisapride shortens intestinal transit time. A lower frequency of diarrhoea is associated with other prokinetics such as metoclopramide.

2.5 Agents Acting in Rheumatological Disorders

2.5.1 Diacerein

Diacerein is a new compound proposed for the treatment of osteoarthritis. In a recent clinical trial, diarrhoea was noted among 37% of patients treated with diacerein compared with only 4% of those receiving placebo.[134] This high frequency is not surprising, since diacerein is closely related to anthraquinone. Diarrhoea was judged to be moderate in the clinical trial, but a recently reported case of severe diarrhoea with dehydration and hypokalaemia in an elderly woman raises the problem of the benefit/risk ratio, as the efficacy of diacerein seems to be relatively moderate.[135]

2.5.2 Colchicine

Colchicine-induced diarrhoea is well known,[136] occurring several hours after oral administration in 80% of patients, and seems to be mediated through stimulated intestinal motility.[136] Long term colchicine therapy has been associated with steatorrhoea[137] and lactose malabsorption.[138] Diarrhoea occurs much more rarely with allopurinol and benzbromarone.[139]

2.5.3 Auranofin

Gold salt therapy is associated with frequent diarrhoea in about 40 to 50% of patients, mostly at the start or during the first months of therapy and diminishing with continued treatment.[140,141] In a prospective study, among the 137 patients with rheumatoid arthritis treated with long term auranofin, 74% reported at least 1 episode of diarrhoea.[141] The diarrhoea usually responded to reduction in the dosage of auranofin or to antidiarrhoeal agents, but 3 to 8% of treated patients had to stop auranofin treatment.[141] It is hypothesised that auranofin induces diarrhoea through inhibition of the Na^+/K^+ ATPase pump of the intestinal mucosa, and by reducing bile acid absorption.[142] These features explain the malabsorptive character of the diarrhoea.[143,144]

Gold-induced enterocolitis is a well recognised, although rare, complication of chrysotherapy, mostly parenteral. Enterocolitis occurs within 3 months of instituting gold therapy, and is characterised by profuse diarrhoea and vomiting with abdominal pain and fever. Petechial changes are prominent on endoscopy.[144] In differential diagnosis, gold-induced enterocolitis has to be distinguished from loose stools occurring during oral gold therapy, and from colitis induced by concomitant application of NSAIDs.[145] No specific therapy is available, except supportive measures and cessation of gold therapy.[146] The overall mortality has been reported to reach 25%.[144] The presence of the HLA-DRB1*0404 allele may be associated with risk for the development of gold-induced enterocolitis.[147]

2.5.4 Sodium Fluoride

Dose-related gastrointestinal adverse effects such as diarrhoea, nausea, vomiting and anorexia occur in about 10 to 40% of patients receiving sodium fluoride therapy. Decreasing the dosage or switching patients to enteric coated or slow release preparations tend to alleviate the adverse effects. Discontinuation of therapy is needed for a few patients.[148,149]

2.5.5 Calcitonin

Calcitonin induces increased secretion of acid and a decrease in the active reabsorption of sodium in the small intestine.[150] This is observed when the plasma concentration of calcitonin exceeds its physiological concentration, and therefore high dosage treatment with calcitonin is likely to induce secretory diarrhoea.[151]

2.5.6 Aminobisphosphonates

Diarrhoea occurs rarely (about 3%) at lower dosages in patients receiving aminobisphosphonates such as alendronate, clodronate or etidronate. The incidence of diarrhoea increases with

the dosage (e.g. to 20% with a daily etidronate dosage of 20 mg/kg) and gastrointestinal upset is sometimes severe enough to require discontinuation of therapy in a few patients.[152,153]

2.6 Oral Hypoglycaemic Agents

2.6.1 α-Glucosidase Inhibitors

α-Glucosidase inhibitors such as acarbose result in dosage-related flatulence, abdominal bloating and diarrhoea caused by malabsorption, which can be severe enough to require withdrawal of treatment. Acarbose reduces intestinal absorption of starch, dextrin and disaccharides by inhibiting the action of the α-glucosidase present in the intestinal brush border, and thus reduces degradation of carbohydrates. A progressive increase in dosage or a restriction in dietary sucrose can reduce these gastrointestinal adverse effects, which occur in about 10 to 33% of patients treated.[154,155] Similar events (e.g. diarrhoea, soft stools) are reported with another α-glucosidase inhibitor, miglitol, and appear to be dosage-dependent.[156]

2.6.2 Biguanides

The major adverse effects of biguanides are gastrointestinal and occur in up to 20% of patients; they include nausea, vomiting and diarrhoea. The mechanism of diarrhoea has not been elucidated, although malabsorption of fat and carbohydrates is suspected.[157] The danger of such diarrhoea is the occurrence of dehydration, which increases the risk of a rare lactic acidosis that affects mainly elderly patients with impaired renal function.[158]

2.7 Laxatives

Laxatives are widely prescribed or obtained over-the-counter to promote defecation and to regularise bowel movements. All classes of laxatives except mineral oil (liquid paraffin) and bulk-forming laxatives (mucilage, bran) induce diarrhoea, which is simply the reflection of an excessively high dosage of laxative.[159] Decreasing the dose or discontinuing the laxative is sufficient to relieve the diarrhoea. Osmotic laxatives, e.g. lactulose, mannitol, lactilol, sorbitol, polyethylene glycol and magnesium salts, result in osmotic diarrhoea.[160-162] Magnesium salts contained in antacids produce a similar diarrhoea when taken in too large doses.[163] Stimulant laxatives produce secretory diarrhoea. These agents, which promote an accumulation of water and electrolytes in the colonic lumen, include phenolphthalein, bisacodyl, oxyphenisatin and derivatives of anthraquinone (e.g. senna, cascara, aloe, rhubarb, dantron). After a few months of ingestion of massive doses of anthracene laxatives, a rectocolic pseudomelanosis can be seen as a dark discoloration of the mucosa. This is generally reversible within several months after drug discontinuation.[164]

A rare complication of laxative abuse is the cathartic colon with severe diarrhoea and hypokalaemia, affecting exclusively women.[4,159] This is the consequence of prolonged and surreptitious consumption of laxatives at cathartic doses, associated with psychiatric disorders. Laxatives involved in this abuse are stimulant laxatives, but also surfactant laxatives such as ricinoleic acid (the active ingredient of castor oil) or docusate sodium (dioctyl sodium sulfosuccinate) and magnesium salts. Mineral oil, mucilage and osmotic laxatives have not been reported to lead to such disease.

The diarrhoea is partly due to a secretory mechanism, recognised clinically as the stools are watery and often voluminous (>1 L/day in many cases). The secretory character is confirmed by the osmolality of the stool, which is close to the osmolality of plasma. Moreover, since the diarrhoea is caused by abnormalities in electrolyte transport through the intestinal mucosa, it usually persists during several days of fasting. An exudative enteropathy with hypoalbuminaemia or steatorrhoea can be associated with the secretory diarrhoea.[165] Potassium depletion is constant, and is often major and symptomatic. Barium enema abnormalities are rarely present but are pathognomonic. They predominate in the ileocaecal region and comprise major colonic haustration disorders, atony of the last loop of the ileum, gaping of the ileocolonic valve and atony of the ascending colon. Endoscopy is mostly normal. The histology of biopsy specimens reveals nonspecific lesions such as atrophy of co-

lonic mucosa with an inflammatory infiltrate of the chorion, marked thickening of the muscular mucous layer and hyperplasia of the nervous myenteric plexus. Diagnosis is difficult, and is usually only established after extensive and negative procedures. Anthraquinone and phenolphthalein can be searched for in the urine and stool. Also, albeit unethical for some, a search of the patient's room for laxatives can be useful, avoiding harmful and useless tests and therapies. Therapeutic decision-making is delicate in this psychiatric context.

2.8 Olsalazine

Olsalazine (azodisalicylate) has recently been developed for treatment of inflammatory bowel disease with the aim of avoiding sulfasalazine-related adverse effects due to the sulfapyridine moiety.[166,167] A major adverse effect of olsalazine is diarrhoea, reported in 12 to 25% of patients.[168,169] Diarrhoea often resolves despite continued drug administration; however, diarrhoea necessitated treatment withdrawal in 12 to 16% of patients during clinical trials.[167,170] 60% of patients receiving pelvic radiation therapy experienced diarrhoea with olsalazine compared with only 14% with placebo.[171]

Olsalazine inhibits the ileal and colonic sodium pump (Na^+/K^+ ATPase), which may enhance ileal and colonic water and electrolyte secretion.[166,169,172] This mechanism is possibly of clinical relevance in patients with severely damaged mucosa. In patients with milder forms of mucosal inflammation, this inhibition is probably of minor importance because of the great capacity of the Na^+/K^+ ATPase and incomplete inhibition, leaving at least 20% of the enzyme activity intact.[166] This latter feature may explain the lower frequency of diarrhoea observed in patients in remission and treated with olsalazine.[173,174] Sulfasalazine and mesalazine (5-aminosalicylic acid) exert similar actions *in vitro*[166,169] or in healthy volunteers,[172] but the frequency of diarrhoea in patients is much lower. Olsalazine may also inhibit ileal bile acid transport, resulting in excess bile acids reaching the colon and in bile acid–induced secretory diarrhoea.[168]

2.9 Pharmacological Agents in Obesity

Orlistat, which belongs to a new class of anti-obesity agents (the lipase inhibitors), inhibits gastric and pancreatic lipases. This inhibition has the dose-dependent effect of decreasing dietary fat absorption (with a maximum of 30% inhibition of fat absorption with a dosage of 120mg 3 times daily) and increasing excretion of triglycerides in the faeces.

Adverse events result from the pharmacodynamic profile of orlistat and are dosage-related. In clinical trials, 60% to >80% of patients treated with orlistat experienced gastrointestinal events related to the induced steatorrhoea. The following adverse events have been reported: fatty or oily stools (21 to 31% of patients), increased defecation (19 to 20%), soft stools (12 to 15%), oily spotting (8 to 18%), liquid stools (7 to 13%), faecal urgency (10%), oily evacuation (6 to 7%), flatus with discharge (3 to 7%), faecal incontinence (2 to 7%), and also flatus and abdominal pain.[175-177] Most events were mild and occurred within the first week of treatment and the incidence was reduced after 12 weeks of therapy.

These events depend on the dietary fat intake: when the fat intake is reduced from 130 to 45g per day, adverse events are similar in placebo and orlistat recipients.[176] Finally, only 2% of patients withdrew from 1 trial because of gastrointestinal-related adverse events.[175] Orlistat reduces the absorption of fat-soluble vitamins, particularly vitamins E and D, when given at higher dosages (120mg 3 times daily) and for a long period, but practical guidelines for vitamin supplementation are not available.

2.10 Antineoplastic Agents

Many antineoplastic agents have been reported to induce diarrhoea in more than 10% of patients, e.g. idarubicin (9 to 22%), epirubicin (13%), pentostatin (10%), mitoguazone (30%), mitoxantrone (up to 16%), docetaxel (8 to 25%), teniposide, flucytosine and fluorouracil.[5] Because of their cyto-

toxic properties, they destroy the intestinal mucosa of the small and large intestine and lead to an abundant diarrhoea, rarely with blood. The mechanism is thought to be exudative and secretory. The risk of diarrhoea is increased when several antineoplastic agents are used within regimens, e.g. 33% of patients treated with a regimen of idarubicin, etoposide and carboplatin reported diarrhoea.[178] Octreotide treatment may be useful in this type of diarrhoea.[179] Pseudomembranous colitis has been reported.[180-183] The clinical presentation and therapy are similar to those for pseudomembranous colitis observed during antimicrobial treatment, but the prognosis is poorer, because of the poorer health of the patients.

2.11 Somatostatin Derivatives

Octreotide is a synthetic analogue of somatostatin. Diarrhoea, loose stools, nausea and abdominal discomfort occur in 5 to 13% of patients receiving octreotide; in some patients, diarrhoea appears to be dosage-related. Octreotide may interfere with the intestinal digestion of fat.[184-186] The frequency of diarrhoea or loose stools rises to 100% of patients after subcutaneous lanreotide therapy.[187]

2.12 Chenodeoxycholic Acid

Mild and transient diarrhoea is the most common adverse event, occurring in 40 to 50% of patients treated with chenodeoxycholic acid. Diarrhoea usually appears during the first weeks of treatment and is dosage-related, as it resolves with reduction in dosage.[188] Chenodeoxycholic acid probably causes diarrhoea by inducing intestinal secretion of fluids or by shortening intestinal transit time.[189] In comparison, ursodeoxycholic acid is better tolerated.[190]

2.13 Hypolipidaemic Drugs

The frequency of diarrhoea during HMG-CoA reductase inhibitor therapy (simvastatin, lovastatin, pravastatin) is less than 5%. A case of colitis and protein-losing enteropathy during simvastatin therapy has been reported.[17] Rechallenge was positive.[17] During cholestyramine therapy, mild steatorrhoea may occur, particularly with the use of dosages of 24 to 30 g/day.[191]

2.14 Drugs Acting on the Central Nervous System

Some recently developed compounds have been reported to induce diarrhoea: sertraline (an antidepressant acting as a serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor[192]); tacrine,[193] donepezil[194] and velnacrine[195] (acetylcholinesterase inhibitors for Alzheimer's disease – up to 14% of patients experienced diarrhoea which rarely interrupted therapy[195]); dexfenfluramine (an anorexigenic agent[196]); riluzole (a new agent for amyotrophic lateral sclerosis[197]); and tolcapone (a catechol-*O*-methyltransferase inhibitor for Parkinson's disease[198]). In some cases, imipramine (a tricyclic antidepressant) and antipsychotic drugs have been associated with haemorrhagic and ulcerated ileitis or colitis during long term treatment,[199-201] and carbamazepine has been associated with lymphocytic or eosinophilic colitis.[16,202]

2.15 Drugs Acting on Chronic Cerebrovascular Insufficiency

Vinburnine belongs to the class of drugs supposed to improve some aspects of chronic cerebrovascular insufficiency. Recently, an observation of liquid diarrhoea associated with histological lesions of lymphocytic colitis occurring at the fifteenth day of treatment with vinburnine was published.[203]

2.16 Isotretinoin

Isotretinoin is efficient in treating acne lesions. One case of severe diarrhoea with blood and mucus, occurring in a young patient a few days after the start of treatment, has been reported.[204] Endoscopy revealed proctosigmoiditis with patchy mucosal inflammation associated with numerous discrete aphthous ulcerations. Histological exami-

nation showed an acute focal superficial inflammatory infiltrate of the mucosa. The diarrhoea resolved promptly on withdrawal of isotretinoin, and rechallenge was positive. The mechanism of the diarrhoea remains unknown.[204]

2.17 Immunosuppressants

Azathioprine, an immunosuppressive agent used to treat inflammatory bowel disease, has been involved in 4 observations of acute and severe diarrhoea appearing after a few days of treatment.[205] Symptoms (abdominal pain, increased number of bowel movements) ceased with discontinuation of the drug. However, the relationship between azathioprine intake and drug-induced diarrhoea is difficult to establish, since the patients treated had pre-existing diarrhoea due to their inflammatory bowel disease.

Two cases of colitis in patients receiving cyclosporin have been published,[206,207] with a positive rechallenge in 1 case.[207]

2.18 Didanosine

Apart from pancreatitis and peripheral neuropathy, the other major adverse event associated with didanosine therapy is diarrhoea, reported in 17 to 28% of patients.[208]

2.19 Artificial Sweeteners

Sugar substitutes often contain sorbitol, mannitol, fructose or magnesium, which can induce diarrhoea if consumption of artificial sweeteners is too high.[162,209] Moreover, sorbitol is present as an inactive ingredient in many prescription and over-the-counter oral liquid medications.[210,211]

3. Diagnosis, Treatment and Prevention of Drug-Induced Diarrhoea

3.1 Diagnosis

The medical history is very important, and a careful drug history must be taken. The clinical examination searches for severity criteria such as fever, rectal emission of blood and mucus, dehydration and bodyweight loss. Establishing a possible relationship between a drug and a case of diarrhoea or colitis can be difficult when the time elapsed between the start of the drug and the onset of symptoms is long, sometimes up to several months or years,[85,87] and the diagnosis can be unrecognised.[212]

Usually, in chronic diarrhoea, an extensive and long work-up is performed.[93] It is helpful to consider a list of the most likely diagnostic possibilities to avoid multiple tests.[213] In clinical practice, endoscopy and biopsy are rarely performed. Patients undergo such procedures only in cases of chronic and/or severe diarrhoea (bloody stools, fever, bodyweight loss). The diagnosis of drug-induced diarrhoea, except for antibacterial-associated diarrhoea, relies on the absence of other obvious aetiologies established by simple tests, on the rapid disappearance of the diarrhoea after withdrawal of the suspected drug, and sometimes on a positive rechallenge. The diagnosis may be evoked by chance by unintentionally stopping a drug, as in the case of a patient hospitalised for severe chronic diarrhoea with bodyweight loss: to perform a colonoscopy, the ticlopidine treatment the patient was receiving was stopped and the diarrhoea disappeared within a few days.[85]

Acute benign diarrhoea is often self-limited and the diagnosis can usually be made by history and physical examination.[214] In severe and/or chronic diarrhoea, some tests should be carried out, unless the diagnosis is apparent (table II).[4,215,216] If these examinations are not helpful, a second panel of tests can be considered (table II). In difficult cases, the diagnostic procedure requires specialised tests, and a trial therapy such as metronidazole or a lactose-free diet is sometimes proposed.[4] After a complete and negative evaluation, almost half of the cases of chronic diarrhoea are likely to be related to surreptitious laxative abuse.[217]

3.2 Treatment

Most of the time, acute diarrhoea simply resolves spontaneously within a few days after withdrawal of the drug or in spite of continuing the

Table II. Diagnostic tests in severe and/or chronic diarrhoea

First panel of tests
Blood examination: haemogram (complete blood count), erythrocyte sedimentation rate, albumin, serum electrolytes, calcaemia, renal function
Stool examination: consistency, frequency and weight per 24 hours, occult blood, leucocytes, ova and parasites, culture for enteric pathogens, culture for *Clostridium difficile* and isolation of toxins if recent antibacterial use
Rectosigmoidoscopy or colonoscopy with biopsies for histology and culture examination have to be considered, especially in patients with bloody diarrhoea
Second panel of tests
Hospitalisation with stool collection carried out for 2 to 3 days to define the frequency of bowel movements, the consistency and weight of stools, the percentage of dry weight, the value of electrolytes, pH, osmolality, osmolality gap, and steatorrhoea, and to search for laxatives (phenolphthalein, anthraquinones, magnesium)
Urine tests to detect aloe, senna and bisacodyl
Blood examination: electrophoresis and immunoelectrophoresis of plasma proteins, amoeba serology, thyroid hormones
D-Xylose absorption if malabsorption is suspected
α_1-Antitrypsin clearance if exudation enteropathy is suspected
Upper endoscopy with duodenal or small intestinal biopsy; plain abdominal radiography and barium studies of the small intestine
Abdominal and pelvic tomodensitometry

treatment. Some cases of diarrhoea are controlled by adjustment of dosage. Similarly, chronic diarrhoea usually ceases when the drug is stopped. Symptomatic treatment consists of diet and oral rehydration therapy. In case of severe diarrhoea, hospitalisation can be necessary for parenteral rehydration therapy and correction of hypokalaemia.[214]

Antiperistaltic agents such as opioid derivatives (e.g. loperamide, diphenoxylate, codeine) can be useful in profuse diarrhoea to slow intestinal transit and thus alleviate the discomfort of patients. These agents should not be used in patients with severe diarrhoea, as they could lead to colic retention of bacteria and toxins and to the development of toxic megacolon, especially if the diarrhoea is related to a change in the microflora.[214]

3.3 Prevention

Before prescribing any relevant drug, patients should be asked whether they have already experienced any intolerance or allergy to certain drugs, and especially drug-induced diarrhoea. If digestive intolerance with a particular drug is reported, an alternative drug should be prescribed.

When considering the prescription of antibacterials, the need for such a prescription should be real. When prescribing antibacterials, care should be taken to select an agent whose spectrum of activity is appropriate for the suspected pathogen. Broad spectrum antibacterials should be reserved for severe infectious diseases or documented infections with an antibiogram (i.e. an *in vitro* study of action of antibacterials upon the selected bacterium in order to select the most appropriate antibacterial).

Dosage and duration of treatment should be adapted to the age of the patient and to hepatic and renal function. Certain types of diarrhoea can be minimised by taking the drug during meals or progressively increasing the dosage. The use of NSAIDs in patients with inflammatory bowel disease should be cautious after consideration of their possible harmful effects.[76]

4. Treatment and Prevention of Pseudomembranous Colitis

Apart from withdrawal of the suspected antibacterial and symptomatic treatment of the diarrhoea, pseudomembranous colitis requires specific antibacterial therapy. This has to be started as soon as the diagnosis is confirmed by the isolation of *C. difficile* or its toxins (tissue culture assay or enzyme immunoassay) in stool.[40,41] Treatment must also be started when a strong suspicion exists, even if the stool examination is negative.

Two antibacterials have been shown to be effective. Oral or parenteral metronidazole is given at a dosage of 250mg 4 times daily for 7 to 10 days.[218] Metronidazole has adverse effects such as metallic taste, dizziness and, more rarely, disulfiram-like effect or sensory neuropathy. Vancomycin is given orally from 125mg 3 times daily to 500mg 4 times daily in severe cases.[33] Vancomycin is well tolerated but its cost is higher than that of metronidazole. Because of increasing resistance of enterococci to vancomycin, it is now recommended that metronidazole should be used first and that vancomycin should be reserved for use in the following situations: severe life-threatening colitis, allergy to metronidazole, pregnancy, and age <10 years.[219] Complications of pseudomembranous colitis may require endoscopic exsufflation or colectomy.

Pseudomembranous colitis presents a risk of relapse, which is seen in 20% of patients.[220] No therapeutic approach has been shown to be really efficient to reduce the rate of relapse. It is recommended not to prescribe any antibacterial for 2 months after an episode of pseudomembranous colitis. Afterwards, if the patient requires an antibacterial, it has been proposed that either metronidazole or vancomycin should be used in combination with the antibacterial.[40]

5. Role of Probiotics

Nonpathogenic micro-organisms (e.g. *Saccharomyces boulardii* or *Lactobacillus*) are often prescribed for prevention or treatment of antibacterial-induced diarrhoea. There is a lack of well conducted clinical trials demonstrating any significant benefits of these probiotics in humans.[221] Their systematic coprescription is useless in treating or preventing antibacterial-induced diarrhoea.[222] *S. boulardii* may be useful in some patients (i.e. elderly, seriously ill and hospitalised patients) with a history of pseudomembranous colitis.[220] During broad spectrum antibacterial treatment in this subset of patients, who present a greater risk of relapse, *S. boulardii* reduces the risk of relapse of pseudomembranous colitis compared with placebo.[220,223] Several cases of systemic fungal infections have been reported after administration of probiotic yeasts.[224-226] Therefore, caution should be advised in the clinical use of these strains in immunocompromised patients until further study is undertaken.[227]

6. Conclusions

New drugs are likely to induce diarrhoea because of their pharmacodynamic properties; such drugs include anthraquinone-related agents (diacerein), α-glucosidase inhibitors (acarbose), lipase inhibitors (orlistat) or cholinesterase inhibitors. The increasing prescription of antibacterials related to eradication of *H. pylori* may also lead to an increase of microbial proliferation and pseudomembranous colitis.

The mechanism of many cases of drug-induced diarrhoea has not yet been elucidated. In a patient presenting with diarrhoea, an accurate medical history is very important, especially the drug history, as it can establish the diagnosis of drug-induced diarrhoea and thereby avoid multiple diagnostic tests.

References

1. Bramble MG, Record CO. Drug-induced gastrointestinal disease. Drugs 1978; 15: 451-63
2. Johnson RA. Adverse reactions in ten years' general practice, computer-analysed. J R Soc Med 1986; 79: 143-6
3. Beaugerie L, Gendre JP. Drug-induced colitis. Med Hyg 1993; 51: 2153-5
4. Fine KD. Diarrhea. In: Feldman M, Scharschmidt BF, Sleisenger MH, editors. Sleisenger and Fordtran's gastrointestinal and liver disease: pathophysiology, diagnosis, management. 6th ed. Philadelphia: WB Saunders, 1998: 128-52
5. Micromedex Inc. Micromedex Healthcare Series New Integrated Index™ [online document]. Available from: www.micromedex.com [accessed 1999 Nov 22]
6. Pariente EA. Drug-induced enteropathies. Gastroenterol Clin Biol 1982; 6: 16-8
7. Ratnaike RN, Jones TE. Mechanisms of drug-induced diarrhoea in the elderly. Drugs Aging 1998; 13: 245-53
8. Longstreth GF, Newcomer AD. Drug-induced malabsorption. Mayo Clin Proc 1975; 50: 284-93
9. Riddell RH, Tanaka M, Mazzoleni G. Non-steroidal antiinflammatory drugs as a possible cause of collagenous colitis: a case-control study. Gut 1992; 33: 683-6
10. Giardiello FM, Hansen FC, Lazenby AJ, et al. Collagenous colitis setting of non steroidal antiinflammatory drugs and antibiotics. Dig Dis Sci 1990; 35: 257-60
11. Beaugerie L, Luboinski J, Brousse N, et al. Drug-induced lymphocytic colitis. Gut 1994; 35: 426-8

12. Duncan HD, Talbot IC, Silk DB. Collagenous colitis and cimetidine. Eur J Gastroenterol Hepatol 1997; 9: 819-20
13. Berrebi D, Sautet A, Flejou JF, et al. Ticlopidine induced colitis: a histopathological study including apoptosis. J Clin Pathol 1998; 51: 280-3
14. Yaziji N, Rassiat E, Michiels C, et al. Modopar-induced lymphocytic colitis. Ann Pathol 1996; 16: 25
15. Bouchet-Laneuw F, Deplaix P, Dumollard JM, et al. Chronic diarrhea secondary to tardyferon and associated to lymphocytic colitis. Gastroenterol Clin Biol 1997; 21: 83-4
16. Anttila VJ, Valtonen M. Carbamazepine-induced eosinophilic colitis. Epilepsia 1992; 33: 119-21
17. Chagnon JP, Cerf M. Simvastatin-induced protein-losing enteropathy. Am J Gastroenterol 1992; 87: 257
18. Bo-Linn GW, Vendrell DD, Lee E, et al. An evaluation of the significance of microscopic colitis in patients with chronic diarrhea. J Clin Invest 1985; 75: 1559-69
19. Weber DJ, Tolkoff-Rubin NE, Rubin RH. Amoxicillin and potassium clavulanate: an antibiotic combination: mechanism of action, pharmacokinetics, antimicrobial spectrum, clinical efficacy and adverse effects. Pharmacotherapy 1984; 4: 122-36
20. Gales MA, Gales BJ. Recognition of severe cefixime-induced diarrhea. Clin Pharm 1993; 12: 881
21. Schwartzberg JE, Maresca RM, Remington JS. Gastrointestinal side effects associated with clindamycin. 1000 consecutive patients. Arch Intern Med 1976; 136: 876-9
22. Bauwens JE, McFarland LV, Melcher MJ, et al. Recurrent *Clostridium difficile* disease following ciprofloxacin use. Ann Pharmacother 1997; 31: 1090
23. Periti P, Mazzci T, Mini E, et al. Adverse effects of macrolide antibacterials. Drug Saf 1993; 9: 346-64
24. Bartlett JG. Antibiotic-associated diarrhea. Clin Infect Dis 1992; 15: 573-81
25. Nord CE, Heimdahl A, Kager L. Antimicrobial induced alterations of the human oropharyngeal and intestinal microflora. Scand J Infect Dis 1986; 49 Suppl.: 64-72
26. McFarland LV. Risk factors for antibiotic-associated diarrhea. Ann Med Interne 1998; 149: 261-6
27. Rao SSC, Edwards CA, Austen CJ, et al. Impaired colonic fermentation of carbohydrate after ampicillin. Gastroenterology 1988; 94: 928-32
28. Clausen MR, Bonnen H, Tvede M, et al. Colonic fermentation to short-chain fatty acids is decreased in antibiotic associated diarrhea. Gastroenterology 1991; 101: 1497-504
29. Cerny A. Side effects and consequences of frequently used antibiotics in clinical practice. Schweiz Med Wochenschr 1996; 126: 528-34
30. Jaimes EC. Lincocinamides and the incidence of antibiotic-associated colitis. Clin Ther 1991; 13: 270-80
31. Thompson JW, Jacobs RF. Adverse effects of newer cephalosporins. Drug Saf 1993; 9: 132-42
32. Moskovitz BL. Clinical adverse effects during ceftriaxone therapy. Am J Med 1984; 77 (Suppl C): 84-8
33. Job ML, Jacobs NF. Drug-induced *Clostridium difficile*-associated disease. Drug Saf 1997; 17: 37-46
34. Pothoulakis C. Pathogenesis of *Clostridium difficile*-associated diarrhoea. Eur J Gastroenterol Hepatol 1996; 8: 1041-7
35. Rolfe RD, Finegold SM. Intestinal beta-lactamase activity in ampicillin-induced *Clostridium difficile* associated ileocolitis. J Infect Dis 1983; 147: 227-35
36. Tedesco FJ. Ampicillin-associated diarrhea. A prospective study. Am J Dig Dis 1975; 4: 295-7
37. Toffler RB, Pingoud EG, Burrel MI. Acute colitis related to penicillin and penicillin derivatives. Lancet 1978; II: 707-9
38. Werth B, Kobler E, Reinhart WH, et al. *Clostridium difficile* associated diarrhea in cephalosporin administration: experiences of the Swiss adverse drug reaction reporting system 1981-1995. Schweiz Med Wochenschr 1997; 89 Suppl.: 5-8
39. Tedesco FJ, Barton RW, Alpers DH. Clindamycin associated colitis. Ann Intern Med 1974; 81: 429-33
40. Fekety R. Guidelines for the diagnosis and management of *Clostridium difficile*-associated diarrhea and colitis. Am J Gastroenterol 1997; 92: 739-50
41. Tabaqchali S, Jumaa P. Diagnosis and management of *Clostridium difficile* infection. BMJ 1995; 310: 1375-80
42. Rubin MS, Bodenstein LE, Kent KC. Severe *Clostridium difficile* colitis. Dis Colon Rectum 1995; 38: 350-4
43. Maignan M, Schuhmacher H, Pierfitte C, et al. Pseudomembranous colitis associated with josamycin. Therapie 1994; 49: 461-2
44. Nawaz A, Mohammed I, Ahsan K, et al. *Clostridium difficile* colitis associated with treatment of *Helicobacter pylori* infection. Am J Gastroenterol 1998; 93: 1175-6
45. McKinley M, Toffler RB. Antibiotic associated hemorragic colitis. Dig Dis Sci 1980; 25: 812-3
46. Blanchi A, Pariente A. Acute hemorrhagic colitis after ingestion of amoxicillin. Gastroenterol Clin Biol 1992; 16: 1012-4
47. Perez-Castrillon JL, Duenas A, Goyeneche MA, et al. Hemorrhagic colitis due to amoxicillin/clavulanate and nasal decongestants? J Clin Gastroenterol 1997; 25: 701
48. Fort E, Sevestre C, Cahiez M, et al. Acute hemorrhagic colitis after oral ingestion of synergistin. Gastroenterol Clin Biol 1993; 17: 231-2
49. Decaux C, Devroede G. Acute colitis related to spiramycin. Lancet 1978; II: 993
50. David XR, Pierrugues R, Michel H. Acute hemorrhagic colitis related to oral administration of cephalosporin. Gastroenterol Clin Biol 1991; 15: 659
51. Bellaiche G, Le Pennec MP, Choudat L, et al. Value of rectosigmoidoscopy with bacteriological culture of colonic biopsies in the diagnosis of post-antibiotic hemorrhagic colitis related to *Klebsiella oxytoca*. Gastroenterol Clin Biol 1997; 21: 764-7
52. Benoit R, Danchequin Dorval E, Loulergue J, et al. Post-antibiotic diarrheas: role of *Klebsiella oxytoca*. Gastroenterol Clin Biol 1992; 16: 860-4
53. Cleau D, humblot S, Jobard JM, et al. Acute right side hemorrhagic colitis with demonstration of *Klebsiella oxytoca* after treatment with amoxicillin. Presse Med 1994; 23: 1879-80
54. Danna PL, Urban C, Bellin E, et al. Role of *Candida* in pathogenesis of antibiotic-associated diarrhea in elderly inpatients. Lancet 1991; 337: 511-4
55. Dobbins WO, Herrero BA, Mansbach DM. Morphologic alterations associated with neomycin induced malabsorption. Am J Med Sci 1968; 255: 63-7
56. Giannella RA, Serumaga J, Walls D, et al. Effect of clindamycin on intestinal water and glucose transport in the rat. Gastroenterology 1981; 80: 907-13
57. Weber FH, Richards RD, McCallum RW. Erythromycin: a motilin agonist and gastrointestinal prokinetic agent. Am J Gastroenterol 1993; 88: 485-90
58. Lees GM, Percy WH. Antibiotic associated colitis: an in vitro investigation of the effects of antibiotics on intestinal motility. Br J Pharmacol 1981; 73: 535-47
59. Lehtola J, Jaunohen P, Kesaniemi A, et al. Effect of erythromycin on the oro-caecal transit time in man. Eur J Clin Pharmacol 1990; 39: 555-8

60. Tomosa S, Kuroume T, Arai H, et al. Erythromycin induces migrating motor complex in human gastrointestinal tract. Dig Dis Sci 1986; 31: 157-61
61. Bjarnason J, MacPherson A. The changing gastrointestinal side effect profile of non steroidal anti-inflammatory drugs. A new approach for the prevention of a new problem. Scand J Gastroenterol 1989; 24: 56-64
62. Davies NM, Can PD. Toxicity of nonsteroidal anti-inflammatory drugs in the large intestine. Dis Colon Rectum 1995; 38: 1311-21
63. Morgan GJ, Poland M, DeLapp RE. Efficacy and safety of nabumetone versus diclofenac, naproxen, ibuprofen, and piroxicam in the elderly. Am J Med 1993; 95 Suppl. 2A: 19-27
64. Bjarnason I, Williams P, Smethurst P, et al. Effect of non-steroidal anti-inflammatory drugs and prostaglandins on the permeability of the human small intestine. Gut 1986; 27: 1292-7
65. Arvanitakis C, Chen GH, Folscroft J, et al. Effects of aspirin on intestinal absorption of glucose, Na and water in man. Gut 1977; 18: 187-90
66. Lapoile E, Bellaiche G, Nouts A, et al. Pseudomembranous colitis after ingestion of diclofenac. Gastroenterol Clin Biol 1988, 22: 100-1
67. Gentric A, Pennec YL. Diclofenac induced pseudomembranous colitis. Lancet 1992; 340: 126-7
68. Kwo PY, Tremaine WJ. Nonsteroidal anti-inflammatory drug-induced enteropathy: case discussion and review of the literature. Mayo Clin Proc 1995; 70: 55-61
69. Bjarnason I, Prouse P, Smith T, et al. Blood and protein loss via small-intestinal inflammation induced by non-steroidal anti-inflammatory drugs. Lancet 1987; II: 711-4
70. Hall RI, Petty AH, Cobden I, et al. Enteritis and colitis associated with mefenamic acid. BMJ 1983; 287: 1182
71. Gibson GR, Withacre EB, Ricotti CA. Colitis induced by non-steroidal anti-inflammatory drugs. Arch Intern Med 1992; 152: 625-32
72. Dao T, Grimaux-Jardin I, Fellous F, et al. Ulcerative colitis secondary to the ingestion of lysine acetylsalicylate. Gastroenterol Clin Biol 1993; 17: 66-7
73. Sturges HF, Krone CL. Ulceration and stricture of the jejunum in a patient on long-term indomethacin therapy. Am J Gastroenterol 1973; 59: 162-9
74. Langmann MJS, Morgan L, Worrall A. Use of anti-inflammatory drugs by patients admitted with small or large bowel perforations and haemorrhage. BMJ 1985; 290: 347-9
75. Bjarnason I, MacPherson AJS. Intestinal toxicity of non-steroidal anti-inflammatory drugs. Pharmacol Ther 1994; 62: 145-57
76. Kaufmann HJ, Taubin HL. Nonsteroidal anti-inflammatory drugs activate quiescent inflammatory bowel disease. Ann Intern Med 1987; 107: 513-6
77. Wilson RG, Smith AN, McIntyre IMC. Complications of diverticular disease and non-steroidal anti-inflammatory drugs: a prospective study. Br J Surg 1990; 77: 1103-4
78. Fang WF, Broughton A, Jacobson ED. Indomethacin-induced intestinal inflammation. Am J Dig Dis 1977; 22: 749-60
79. Rutherford D, Stockdill G, Hamer-Hodges DW, et al. Proctocolitis induced by salicylate. BMJ 1984; 288: 794
80. Chakraborty TK, Bhatia D, Heading RC, et al. Salicylate induced exacerbation of ulcerative colitis. Gut 1987; 28: 613-5
81. Barnejee AK. Enteropathy induced by non-steroidal anti-inflammatory drugs often subclinical but may mimic Crohn's disease. BMJ 1989; 298: 1539-40
82. Bridges AJ, Marshall JB, Diaz-Arias AA, et al. Acute eosinophilic colitis and hypersensitivity reaction associated with naproxen therapy. Am J Med 1990; 89: 526-7
83. Guedon C, Bruna T, Ducrotté P, et al. Severe diarrhea caused by Ticlid associated with disorders of small intestine motility. Gastroenterol Clin Biol 1989; 13: 934-7
84. Giardina MG, Matarazzo M, Cacciatore L, et al. Ticlopidine can cause chronic diarrhea. Lancet 1984; I: 407
85. Chassany O, Bacq Y, Metman EH, et al. Severe chronic diarrhea during treatment with ticlopidine. Gastroenterol Clin Biol 1989; 13: 950
86. Fraga MD, Garcia B, Agud JL, et al. Severe chronic diarrhea induced by ticlopidine. Ann Pharmacother 1996; 30: 1496
87. Mansoor GA, Aziz K. Delayed chronic diarrhea and weight loss possibly due to ticlopidine therapy. Ann Pharmacother 1997; 31: 870-2
88. Ruget O, Burtin P, Cerz H, et al. Chronic diarrhea associated with villous atrophy and lymphocytic gastritis caused by ticlopidine. Gastroenterol Clin Biol 1992; 16: 290
89. Swine C, Cornette P, Van Pee D, et al. Ticlopidine, diarrhea and lymphocytic colitis. Gastroenterol Clin Biol 1998 ; 22 : 475-6
90. Brigot C, Courillon-Mallet A, Roucayrol AM, et al. Lymphocytic colitis and ticlopidine. Gastroenterol Clin Biol 1998; 22: 361-2
91. Martinez Aviles P, Gisbert-Moya C, Berbegal-Serra J, et al. Ticlopidine-induced lymphocytic colitis. Med Clin Barc 1996; 106: 307
92. Cohen IS, Jick H, Cohen SI, et al. Adverse reactions to quinidine in hospitalized patients: findings based on data from the Boston Collaborative Drug Surveillance Program. Prog Cardiovasc Dis 1977; 20: 152-63
93. Auricchio RJ. Cardiac arrhythmias. In: Young LY, Koda-Kimble MA, editors. Applied therapeutics: the clinical use of drugs, 4th ed. Vancouver: Applied Therapeutics, 1988
94. Romankiewicz JA, Reidenberg M, Drayer D, et al. The noninterference of aluminium hydroxide gel with quinidine sulphate absorption: an approach to control quinidine-induced diarrhea. Am Heart J 1978; 96: 518-20
95. Rudusky BM. Cholestyramine therapy for quinidine-induced diarrhea. Case reports. Angiology 1997; 48: 173-6
96. Horvath F, Marbury TC, Uhlemann ER, et al. Severe diarrhea secondary to propranolol. South Med 1979; 72: 367-8
97. Robinson JD, Burtner DE. Severe diarrhea secondary to propranolol. Drug Intell Clin Pharm 1981; 15: 49-50
98. Rolachon A, Bichard P, Kezachian G, et al. Chronic diarrhea caused by isradipine. Gastroenterol Clin Biol 1993; 17: 310-1
99. Hedner T. Calcium channel blockers: spectrum of side effects and drug interactions. Acta Pharmacol Toxicol 1986; 58 Suppl. 2: 119-30
100. Quart BD, Guglielmo BJ. Prolonged diarrhea secondary to methyldopa therapy. Drug Intell Clin Pharm 1983; 17: 462
101. Gloth FM, Busby MJ. Methyldopa-induced diarrhea: case of iatrogenic diarrhea leading to request for nursing home replacement. Am J Med 1989; 87: 480-1
102. Graham CF, Gallagher K, Jones JK. Acute colitis with methyldopa. N Engl J Med 1981; 304: 1044-5
103. Shneerson JM, Gazzard BJ. Reversible malabsorption caused by methyldopa. BMJ 1977; 2: 1456-7
104. Mahdyoon H, Battilana G, Rosman H, et al. The evolving pattern of digoxin intoxication: observations at a large urban hospital from 1980-1988. Am Heart J 1990; 120: 1189-94
105. Andrews PA, Wilkinson PR. Diarrhoea as a side effect of digoxin. BMJ 1990; 301: 1398
106. Bourhis T, Riard P, Danel V, et al. Digitalis poisoning with severe ischemic colitis: a favorable course after treatment with specific antibodies. Gastroenterol Clin Biol 1990; 14: 95
107. Bouaniche M, Chassagne P, Landrin I, et al. Lymphocytic colitis caused by Cyclo 3 Fort. Rev Med Int 1996; 17: 776-8

108. Thomas-Anterion C, Guy C, Vial F, et al. Unexplained chronic diarrhea. A propos of 4 new cases under Cyclo 3 Fort and review of the literature. Rev Med Interne 1993; 14: 215-7
109. Ouyahya F, Codjovi P, Machet MC, et al. Diarrhea induced by Cyclo 3 Fort and lymphocytic colitis. Gastroenterol Clin Biol 1993; 17: 65-6
110. Pierrugues R, Saingra B. Lymphocytic colitis and Cyclo 3 Fort: 4 new cases. Gastroenterol Clin Biol 1996; 20: 916-7
111. Maechel H. Cirkan-induced chronic diarrhea. Gastroenterol Clin Biol 1992; 16: 373
112. Raoul JL, Dautreme S, Heresbach N, et al. Chronic diarrhea during treatment with Veinotonyl 75. Ann Gastroenterol Hepatol 1994; 30: 25
113. Hastier P, Bianchi D, Chichmanian RM, et al. Chronic diarrhea secondary to Veinamitol. Therapie 1994; 49: 148-9
114. Widgren S, de Peyer R, Geissbuhler P, et al. Enterocolitis due to a saponin-containing drug. A propos of a case. Schweiz Med Wochenschr 1994; 124: 313-8
115. Piper DW. A comparative overview of the adverse effects of antiulcer drugs. Drug Saf 1995; 12: 120-38
116. Yen L. Cimetidine-induced diarrhea. Drug Intell Clin Pharm 1985; 19: 185
117. Beaugerie L, Patey N, Brousse N. Ranitidine, diarrhea, and lymphocytic colitis. Gut 1995; 37: 708-11
118. Beaugerie L, Berrebi D, Dikov D, et al. Epithelial apoptosis a very early marker of drug-induced colitis. The example of ranitidine. Gastroenterol Clin Biol 1996; 20: 918-9
119. Duncan HD, Talbot IC, Silk DB. Collagenous colitis and cimetidine. Eur J Gastroenterol Hepatol 1997; 9: 819-20
120. Field R, Meyer GW. Diarrhea from cimetidine. N Engl J Med 1978; 299: 262
121. Leufkens H, Claessens A, Heerdink E, et al. A prospective follow-up study of 5669 users of lansoprazole in daily practice. Aliment Pharmacol Ther 1997; 11: 887-97
122. Rachmilewitz D. Prostaglandins and diarrhea. Dig Dis Sci 1980; 25: 897-8
123. Silverstein FE, Graham DY, Senior JR, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. Ann Intern Med 1995; 123: 241-9
124. Graham DY, White RH, Moreland LW, et al. Duodenal and gastric ulcer prevention with misoprostol in arthritis patients taking NSAIDs. Ann Intern Med 1993; 119: 257-62
125. Herting RL, Clay GA. Overview of clinical safety with misoprostol. Dig Dis Sci 1985; 30 Suppl.: 185S-93S
126. Bocanegra TS, Weaver AL, Tindall EA, et al. Diclofenac/misoprostol compared with diclofenac in the treatment of osteoarthritis of the knee or hip: a randomized, placebo controlled trial. Arthrotec osteoarthritis study group. J Rheumatol 1998; 25: 1602-11
127. Gagnier P. Review of the safety of diclofenac/misoprostol. Drugs 1993; 45 Suppl.: 31-5
128. Davis R, Yarker YE, Goa KL. Diclofenac/misoprostol: a review of its pharmacology and therapeutic efficacy in painful inflammatory conditions. Drugs Aging 1995; 7: 372-93
129. Melo Gomes JA, Roth SH, Zeeh J, et al. Double-blind comparison of efficacy and gastroduodenal safety of diclofenac/misoprostol, piroxicam, and naproxen in the treatment of osteoarthritis. Ann Rheum Dis 1993; 52: 881-5
130. Bright-Asare P. Treatment of duodenal ulcer with enprostil, a prostaglandin E2 analog. Am J Med 1986; 81: 64-8
131. Jain JK, Mishell DR. A comparison of intravaginal misoprostol with prostaglandin E2 for termination of second-trimester pregnancy. N Engl J Med 1994; 331: 290-3
132. Castell DO, Sigmund C, Patterson D, et al. Cisapride 20 mg b.i.d. provides symptomatic relief of heartburn and related symptoms of chronic mild to moderate gastroesophageal reflux disease. CIS-USA-52 investigator group. Am J Gastroenterol 1998; 93: 547-52
133. Wiseman LR, Faulds D. Cisapride. An updated review of its pharmacology and therapeutic efficacy as a prokinetic agent in gastrointestinal motility disorders. Drugs 1994; 47: 116-52
134. Nguyen M, Dougados M, Berdah L, et al. Diacerhein in the treatment of osteoarthritis of the hip. Arthritis Rheum 1994; 37: 529-36
135. Blondon H, Bikart I, Bergmann JF. Severe diarrhea with hypokalemia attributed to diacetylrhein. Gastroenterol Clin Biol 1995; 19: 851-2
136. Verne GN, Eaker EY, Davis RH, et al. Colchicine is an effective treatment for patients with chronic constipation: an open-label trial. Dig Dis Sci 1997; 42: 1959-63
137. Ehrenfeld M, Levy M, Sharon P, et al. Gastrointestinal effects of long-term colchicine therapy in patients with recurrent polyserositis (familial Mediterranean fever). Dig Dis Sci 1982; 27: 723-7
138. Fradkin A, Yahav J, Zemer D, et al. Colchicine-induced lactose malabsorption in patients with familial Mediterranean fever. Isr J Med Sci 1995; 31: 616-20
139. Chen B, Shapira J, Ravid M, et al. Steatorrhea induced by allopurinol. BMJ 1982; 284: 1914
140. Furst DE. Mechanism of action, pharmacology, clinical efficacy and side effects of auranofin. An orally administered organic gold compound for the treatment of rheumatoid arthritis. Pharmacotherapy 1983; 3: 284-98
141. Wallin BA, McCafferty JP, Fox MJ, et al. Incidence and management of diarrhea during long term auranofin therapy. J Rheumatol 1988; 15: 1755-8
142. Magaro M, Altomonte L, Mirone L, et al. Effect of oral gold salt therapy on bile acid absorption in rheumatoid arthritis patients. Clin Rheumatol 1990; 9: 42-7
143. Gerster JC, Kalbermatten A, Peyer R, et al. Toxic reactions to gold salts with severe enterocolitis in a patient with rheumatoid arthritis. Schweiz Med Wochenschr 1976; 106: 1606-8
144. Jackson CW, Haboubi NY, Whorwell PJ, et al. Gold induced enterocolitis. Gut 1986; 27: 452-6
145. Bross-Bach U, Saal JG, Hartmann F, et al. Ulcerative colitis caused by oral gold therapy in rheumatoid arthritis. Z Rheumatol 1987; 46: 201-4
146. Marcuard SP, Ehrinpreis MN, Fitter WF. Gold induced ulcerative proctitis: report and review of the literature. J Rheumatol 1987; 14: 142-4
147. Evron E, Brautbar C, Becker S, et al. Correlation between gold-induced enterocolitis and the presence of the HLA-DRB1*0404 allele. Arthritis Rheum 1995; 38: 755-9
148. Pitt P, Berry H. Fluoride treatment in osteoporosis. Postgrad Med J 1991; 67: 323-6
149. Pak CY, Sakhaee K, Gallagher C, et al. Attainment of therapeutic fluoride levels in serum without major side effects using a slow-release preparation of sodium fluoride in postmenopausal osteoporosis. J Bone Miner Res 1986; 1: 563-71
150. Gray TK, Brannan P, Juan D, et al. Ion transport changes during calcitonin-induced intestinal secretion in man. Gastroenterology 1976; 71: 392-8
151. Zorzin L, Capone M. Postmenopausal osteoporosis: therapeutic and side effects of different calcitonins. Curr Ther Res 1984; 36: 473-82
152. Luzzani M, Vidili MG, Rissotto R, et al. Disodium clodronate in the treatment of pain due to bone metastases. Int J Clin Pharm Res 1990; 10: 243-6

153. Khairi MR, Altman RD, DeRosa GP, et al. Sodium etidronate in the treatment of Paget's disease of bone. A study of long-term results. Ann Intern Med 1977; 87: 656-63
154. Federlin KF, Mehlburger L, Hillebrand I, et al. The effect of two new glucosidase inhibitors on blood glucose in healthy volunteers and in type 2 diabetics. Acta Diabetol Lat 1987; 24: 213-21
155. Hollander P. Safety profile of acarbose, an alpha-glucosidase inhibitor. Drugs 1992; 44 Suppl. 2: 47-53
156. Johnston PS, Feig PU, Coniff RF, et al. Long-term titrated-dose alpha-glucosidase inhibitor in non-insulin-requiring Hispanic NIDDM patients. diabetes Care 1998; 21: 409-15
157. Melchior WR, Jaber LA. Metformin: an antihyperglycemic agent for treatment of type 2 diabetes. Ann Pharmacother 1996; 30: 158-64
158. McGuinness ME, Talbert RL. Phenformin-induced lactic acidosis: a forgotten adverse drug reaction. Ann Pharmacother 1993; 27: 1183-7
159. Curry CE, Tatum-Butler D. Laxative products. In: Covington TR, editor. Handbook of nonprescription drugs, 10th ed. Washington, DC: American Pharmaceutical Association, 1993: 219-33
160. Chusid MJ, Chusid JA. Diarrhea induced by sorbitol. J Pediatr 1981; 99: 326
161. Hammer HF, Santa Ana CA, Schiller LR, et al. Studies of osmotic diarrhea induced in normal subjects by ingestion of polyethylene glycol and lactulose. J Clin Invest 1989; 84: 1056-62
162. Reele SB, Chodos DJ. Sorbitol induced diarrheal illness model. Int J Clin Pharmacol Ther Toxicol 1985; 23: 403-5
163. Strom M. Antacid side-effects on bowel habits. Scand J Gastroenterol 1982; 17 Suppl. 75: 54-5
164. Anonymous. Senna and pseudomelanosis coli. Pharmacology 1992; 44 Suppl. 1: 33-5
165. Nataf C, Desmazures C, Giraudeaux V, et al. Laxative-induced intestinal protein loss in normal subjects. Gastroenterol Clin Biol 1981; 5: 187-92
166. Scheurlen C, Allgayer H, Kruis W, et al. Effect of olsalazine and mesalazine on human ileal and colonic (Na^+/K^+)-ATPase. A possible diarrhogenic factor? Clin Invest 1993; 71: 286-9
167. Wright JP, O'Keefe EA, Cuming L, et al. Olsalazine in maintenance of clinical remission in patients with ulcerative colitis. Dig Dis Sci 1993; 38: 1837-42
168. Chawla A, Karl PI, Reich RN, et al. Effect of olsalazine on sodium-dependent bile acid transport in rat ileum. Dig Dis Sci 1995; 40: 943-8
169. Pamukcu R, Hanauer SB, Chang EB. Effect of disodium azodisalicylate on electrolyte transport in rabbit ileum and colon in vitro. Comparison with sulfasalazine and 5-aminosalicylic acid. Gastroenterology 1988; 95: 975-81
170. Travis SP, Tysk C, de Silva HJ, et al. Optimum dose of olsalazine for maintaining remission in ulcerative colitis. Gut 1994; 35: 1282-6
171. Martenson JA, Hyland G, Moertel CG, et al. Olsalazine is contraindicated during pelvic radiation therapy: results of a double-blind, randomized clinical trial. Int J Radiat Oncol Biol Phys 1996; 35: 299-303
172. Raimundo AH, Patil DH, Frost PG, et al. Effects of olsalazine and sulphasalazine on jejunal and ileal water and electrolyte absorption in normal human subjects. Gut 1991; 32: 270-74
173. Kruis W, Judmaier G, Kayasseh L, et al. Double-blind dose-finding study of olsalazine versus sulphasalazine as maintenance therapy for ulcerative colitis. Eur J Gastroenterol Hepatol 1995; 7: 391-6
174. Nilsson A, Danielsson A, Lofberg R, et al. Olsalazine versus sulphasalazine for relapse prevention in ulcerative colitis: a multicenter study. Am J Gastroenterol 1995; 90: 381-7
175. Van Gaal LF, Broom JI, Enzi G, et al. Efficacy and tolerability of orlistat in the treatment of obesity: a 6-month dose-ranging study. Eur J Clin Pharmacol 1998; 54: 125-32
176. Sjôstrôm L, Rissanen A, Andersen T, et al. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. Lancet 1998; 352: 167-73
177. McNeely W, Benfield P. Orlistat. Drugs 1998; 56: 241-9
178. Bow EJ, Gallant GJ, Woloschuk D, et al. Remission induction therapy of untreated acute myeloid leukemia using a non-cytarabine-containing regimen of idarubicin, etoposide, and carboplatin. Cancer 1998; 83: 1344-54
179. Cascinu S, Fedeli A, Fedeli SL, et al. Octreotide versus loperamide in the treatment of fluorouracil-induced diarrhea: a randomized trial. J Clin Oncol 1993; 11: 148-51
180. Jarvis B, Shevchuk YM. Recurrent *Clostridium difficile* diarrhea associated with mitoxantrone and etoposide: a case report and review. Pharmacotherapy 1997; 17: 606-11
181. Anand A, Glatt AE. *Clostridium difficile* infection associated with antineoplastic chemotherapy: a review. Clin Infect Dis 1993; 17: 109-13
182. Husain A, Aptaker L, Spriggs DR, et al. Gastrointestinal toxicity and *Clostridium difficile* diarrhea in patients treated with paclitaxel-containing chemotherapy regimens. Gynecol Oncol 1998: 71: 104-7
183. Cudmore MA, Silva J, Fekety R, et al. *Clostridium difficile* colitis associated with cancer chemotherapy. Arch Intern Med 1982; 142: 333-5
184. Jackson IM, Barnard LB, Lamberton P. Role of a long-acting somatostatin analogue (SMS 201-995) in the treatment of acromegaly. Am J Med 1986; 81: 94-101
185. Ho PJ, Boyaji LD, Greenstein E, et al. Effect of chronic octreotide treatment on intestinal absorption in patients with acromegaly. Dig Dis Sci 1993; 38: 309-15
186. Nakamura T, Kudoh K, Takebe K, et al. Octreotide decreases biliary and pancreatic exocrine function, and induces steatorrhea in healthy subjects. Intern Med 1994; 33: 593-6
187. Kuhn JM, Legrand A, Ruiz JM, et al. Pharmacokinetic and pharmacodynamic properties of a long-acting formulation of the new somatostatin analogue, lanreotide, in normal healthy volunteers. Br J Clin Pharmacol 1994; 38: 213-9
188. Maton PN, Iser JH, Reuben A, et al. Outcome of chenodeoxycholic acid (CDCA) treatment in 125 patients with radiolucent gallstones. Medicine 1982; 61: 86-97
189. Kruis W, Haddad A, Phillips SF. Chenodeoxycholic and ursodeoxycholic acids alter motility and fluid transit in the canine ileum. Digestion 1986; 34: 185-95
190. Sackmann M, Paulezki J, Aydemir U, et al. Efficacy and safety of ursodeoxycholic acid for dissolution of gallstone fragments: comparison with the combination of ursodeoxycholic acid and chenodeoxycholic acid. Hepatology 1991; 14: 1136-41
191. Knodel LC, Talbert RL. Adverse effects of hypolipidaemic drugs. Med Toxicol 1987; 2: 10-32
192. Lane R, Baldwin D. Selective serotonin reuptake inhibitor-induced serotonin syndrome: review. J Clin Psychopharmacol 1997; 17: 208-21
193. Gracon SI, Knapp MJ, Berghoff WG, et al. Safety of tacrine: clinical trials, treatment IND, and postmarketing experience. Alzheimer Dis Assoc Disord 1998; 12: 93-101
194. Rogers SL, Doody RS, Mohs RC, et al. Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. Donepezil study group. Arch Intern Med 1998; 158: 1021-31

195. Antuono PG. Effectiveness and safety of velnacrine for the treatment of Alzheimer's disease. A double-blind, placebo-controlled study. Mentane study group. Arch Intern Med 1995; 155: 1766-72
196. Bever KA, Perrry PJ. Dexfenfluramine hydrochloride: an anorexigenic agent. Am J Health Syst Pharm 1997; 54: 2059-72
197. Wagner ML, Landis BE. Riluzole: a new agent for amyotrophic lateral sclerosis. Ann Pharmacother 1997; 31: 738-44
198. Waters CH, Kurth M, Bailey P, et al. Tolcapone in stable Parkinson's disease: efficacy and safety of long-term treatment. Tolcapone stable study group. Neurology 1998; 50 Suppl. 5: 39-45
199. Labayle D, Delas N, Pariente A, et al. Severe psychiatric disorders associated with severe acute colitis. Gastroenterol Clin Biol 1992; 16: 639-43
200. Basse P. Ischemic colitis complicating imipramine overdose and alcohol ingestion. Eur J Surg 1992; 158: 187-8
201. Meya U, Moller B, Renfordt E, et al. A case of perazine-induced enteritis. Allergy or pseudoallergy? Pharmacopsychiatry 1985; 18: 263-6
202. Mahajan L, Wyllie R, Goldblum J. Lymphocytic colitis in a pediatric patient: a possible adverse reaction to carbamazepine. Am J Gastroenterol 1997; 92: 2126-7
203. Chauveau E, Prignet JM, Carloz E, et al. Lymphocytic colitis secondary to ingestion of vinburnine (Cervoxan). Gastroenterol Clin Biol 1998; 22: 362
204. Martin P, Manley PN, Depew WT, et al. Isotretinoin-associated proctosigmoiditis. Gastroenterology 1987; 93: 606-9
205. Cox J, Daneshmend TK, Hawkey CJ, et al. Devastating diarrhea caused by azathioprine: management difficulty in inflammatory bowel disease. Gut 1988; 29: 686-8
206. Murphy EA, Morris AJ, Walker E, et al. Cyclosporine A induced colitis and acquired selective IgA deficiency in a patient with juvenile chronic arthritis. J Rheumatol 1993; 20: 1397-8
207. Bowen JR, Sahi S. Cyclosporin induced colitis. BMJ 1993; 307: 484
208. Pike IM, Nicaise C. The didanosine expanded access program: safety analysis. Clin Infect Dis 1993; 16 Suppl. 1: 63-8
209. Lieb J, Kazienko DJ. Lactose filler as a cause of 'drug-induced' diarrhea. N Engl J Med 1978; 299: 314
210. Shelly MS. Iatrogenic diarrhea caused by sorbitol. J Fam Pract 1993; 36: 95-6
211. Hill DB, Henderson LM, McClain CJ. Osmotic diarrhea induced by sugar-free theophylline solution in critically ill patients. J Parenter Enterol Nutr 1991; 15: 332-6
212. Spreux A, Rodriguez A, Chichmanian RM. Case reports on drug-induced chronic diarrhea. An often unrecognized etiology? Therapie 1993; 48: 494-5
213. Talal AH, Murray JA. Acute and chronic diarrhea. How to keep laboratory testing to a minimum. Postgrad Med 1994; 96: 30-8
214. Bennett RG, Greenough WB. Approach to acute diarrhea in the elderly. Gastroenterol Clin North Am 1993; 22: 517-33
215. Donowitz M, Kokke FT, Saidi R. Evaluation of patients with chronic diarrhea. N Engl J Med 1995; 332: 725-9
216. Duncan A, Cameron A, Stewart MJ, et al. Diagnosis of the abuse of magnesium and stimulant laxatives. Ann Clin Biochem 1991; 28: 568-73
217. Read NW, Krjs GJ, Read MG, et al. Chronic diarrhea of unknown origin. Gastroenterology 1980; 78: 264-71
218. Wenisch C, Parschalk B, Hasenhundl M, et al. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of *Clostridium difficile*-associated diarrhea. Clin Infect Dis 1996; 22: 813-8
219. Hospital Infection Control Advisory Committee. Recommendations for preventing the spread of vancomycin-resistant enterococci. Am J Infect Control 1995; 23: 87-94
220. Fekety R, McFarland LV, Surawicz CM, et al. Recurrent *Clostridium difficile* diarrhea: characteristics of and risk factors for patients enrolled in a prospective, randomized, double-blinded trial. Clin Infect Dis 1997; 24: 324-33
221. Lewis SJ, Freedman AR. Review article: the use of biotherapeutic agents in the prevention and treatment of gastrointestinal disease. Aliment Pharmacol Ther 1998; 12: 807-22
222. Lewis SJ, Potts LF, Barry RE. The lack of therapeutic effect of *Saccharomyces boulardii* in the prevention of antibiotic-related diarrhoea in elderly patients. J Infect 1998; 36: 171-4
223. McFarland LV, Surawicz CM, Greenberg RN, et al. A randomized placebo-controlled trial of *Saccharomyces boulardii* in combination with standard antibiotics for *Clostridium difficile* disease. JAMA 1994; 271: 1913-8
224. Fredenucci I, Chomarat M, Boucaud C, et al. *Saccharomyces boulardii* fungemia in a patient receiving Ultra-levure therapy. Clin Infect Dis 1998; 27: 222-3
225. Viggiano M, Badetti C, Bernini V, et al. *Saccharomyces boulardii* fungemia in a patient with severe burns. Ann Fr Anesth Reanim 1995; 14: 356-8
226. Bassetti S, Frei R, Zimmerli W. Fungemia with *Saccharomyces cerevisiae* after treatment with *Saccharomyces boulardii*. Am J Med 1998; 105: 71-2
227. McCullough MJ, Clemons KV, McCusker JH, et al. Species identification and virulence attributes of *Saccharomyces boulardii* (nom. inval.). J Clin Microbiol 1998; 36: 2613-7

Correspondence and reprints: Dr *Olivier Chassany*, Service de Médecine Interne A, Hôpital Lariboisière, 2 rue Ambroise Paré, 75475 Paris Cedex 10, France.
E-mail: olivier.chassany@lrb.ap-hop-paris.fr