

Colonic Toxicity of Administered Drugs and Chemicals

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Although uncommon, medication-induced colonotoxicity is important to recognize because medication cessation generally leads to prompt clinical improvement, while medication continuation results in disease exacerbation. This review categorizes the association between medications and colonotoxicity as "well-established" or "probable," according to the following criteria: total number of reported cases, number of different research groups reporting an association, experimental and pharmacologic evidence of an association, and validity of an association in each reported case. Cocaine, ergotamine, estrogen, sodium polystyrene, alosetron, amphetamines, pseudoephedrine, and vasopressin are associated with colonic ischemia. The mechanisms include vasospasm, thrombogenesis, and shunting of blood from mesenteric vessels. Narcotics, phenothiazines, vincristine, atropine, nifedipine, and tricyclic antidepressants are associated with colonic pseudo-obstruction. The mechanisms include antagonizing prokinetic neurotransmitters, stimulating antikinetic neurotransmitters, promoting dysmotility, relaxing smooth muscle, and injuring enteric neurons. Numerous antibiotics are associated with pseudomembranous colitis; ampicillin is associated with hemorrhagic colitis; chemotherapy is associated with neutropenic colitis; and deferoxamine is associated with *Yersinia enterocolitis*. Mechanisms of these toxicities include altering normal bowel flora, weakening immunologic defenses, promoting microorganism virulence, and mucosal injury. Gold compounds, nonsteroidal antiinflammatory drugs, alpha-methyldopa, salicylates, and sulfasalazine are associated with an inflammatory or cytotoxic colitis. The mechanisms include direct mucosal cytotoxicity, antimetabolite effects, or drug allergy. Nonsteroidal antiinflammatory drugs, cyclo 3 fort, flutamide, lansoprazole, and ticlopidine are associated with lymphocytic colitis. The mechanisms include immunologic activation or attenuated immunologic defenses. Chronic cathartic use leads to colonic hypomotility and abdominal distention. Intrarectally administered corrosive compounds can produce a toxic colitis.

INTRODUCTION

Although uncommon, medication-induced colonotoxicity is important to understand and recognize because medication withdrawal usually leads to prompt clinical improvement, whereas medication continuation results in disease exacerbation. The clinician finds the literature on medication-induced colonotoxicity to be relatively inaccessible because it is often scattered as single- or two-case reports published in obscure journals and to be relatively difficult to interpret because reported associations are often not substantiated by exclusion of other etiologies, medication rechallenge, or statistical analysis. Moreover, the previously published reviews of this subject, while excellent, are now outdated as they were published in this journal 19 or 10 yr ago (1, 2).

This clinically oriented review of medication-induced colonotoxicity updates these previous reviews, assembles the individual case reports, critically analyzes the literature to exclude coincidental relationships, and synthesizes the reported cases to describe the clinical presentation, diagnosis, and therapy. Medication-associated colonotoxicity is categorized as well-established or probable, according to the following criteria: total number of reported cases, number of independent (different) research groups reporting an association, and plausibility of an association based on experimental and pharmacologic studies. Furthermore, the validity of an association in each reported case is evaluated by the temporal

relationship between medication initiation and onset of toxicity, documentation of colonotoxicity, relationship between medication cessation and toxicity reversal, effect of medication rechallenge, and exclusion of confounding causes of colonotoxicity.

METHODS

Articles on this subject were identified by analysis of: (a) all references cited in the review by Cappell and Simon (2) published in this journal in 1993; (b) all references cited in the review article by Fortson and Tedesco (1) published in this journal in 1984; (c) files maintained by the study author containing more than another 150 articles on the subject; (d) MEDLINE computerized searches using key words for colonic diseases and disorders, such as colitis, colonic ischemia, colonic pseudo-obstruction, or enterocolitis, and key words for drug-induced injury such as drugs, iatrogenic disease, toxicity, or colonic injury; and (e) consultation with both standard and obscure reference books in gastroenterology. To provide a concise and user friendly review for the busy clinician, only one-fourth of the more than 600 articles identified and reviewed in this process are cited as references, and the reviewed information is largely summarized in tabular form. Individual articles are prioritized herein for citation as references based on the number of cases reported,

quality of the analysis of the reported cases, extensiveness of the literature review, and recentness of the publication.

COLONIC ISCHEMIA

Before attributing colonic ischemia to a medication (Table 1) it is necessary to exclude other risk factors for ischemia, such as valvular heart disease, atherosclerotic heart disease, arrhythmias, hypotension, and hypercoagulopathy. Medications can cause colonic ischemia by vasospasm due to neuronal stimulation (*e.g.*, cocaine), by promoting thrombosis due to hormonal effects (*e.g.*, estrogen), or by extrinsic compression due to fibrosis (*e.g.*, methysergide). Other drugs may promote colonic ischemia by shunting blood away from the mesenteric vasculature (*e.g.*, digitalis), by decreasing fluid volume (*e.g.*, diuretics), or by unknown mechanisms. The clinical presentation of medication-induced colonic ischemia is variable and depends upon the severity of the ischemia, the particular affected mesenteric vessel, and the interval between the event and the clinical presentation. The abdominal pain is frequently severe and disproportionate to the clinical signs. Other clinical findings include pyrexia, abdominal tenderness, involuntary guarding, hypoactive bowel sounds,

abdominal distention, bloody stools, and leukocytosis. Abdominal roentgenography may show mucosal thumbprinting, colonic spasm, bowel dilation, pneumatosis coli, or pneumoperitoneum. Colonoscopy may reveal friable, erythematous, edematous, ulcerated, hemorrhagic, or dusky mucosa. Segmental involvement is typical.

Well-Established Associations

COCAINE. Cocaine produces potent mesenteric vasoconstriction by stimulating noradrenergic receptors. Twenty-eight patients developed intestinal ischemia after intravenous, intranasal, or oral cocaine administration (3, 4). Patients frequently require laparotomy for gangrenous bowel (3).

ERGOTAMINE. Ergotamine, used to treat migraine headaches, can cause local ischemia due to vasospasm (1). Eighteen patients developed proctitis after administration of ergotamine suppositories (5, 6). Sigmoidoscopy shows shallow, geographic rectal ulcers. These ulcers usually rapidly resolve after discontinuation of the medication. Complications include rectal strictures or rectovaginal fistulas (5).

Table 1. Medications Causing Colonic Ischemia

Medication	Proposed Mechanism	No. of Cases Reported	References
Well-established associations			
Cocaine	Vasoconstriction due to noradrenergic stimulation	28	(3, 4)
Ergotamine	Vasospasm	19	(5, 6)
Estrogens (with progesterone)	Thrombosis due to hypercoagulability	Numerous	(7)
Sodium polystyrene (kayexalate) in sorbitol	Electrolyte shifts due to kayexalate or hypertonicity of sorbitol	>25	(8, 9)
Probable associations			
Alosetron	Compromised mucosal perfusion due to increased intraluminal pressure with fecal impaction and vasoconstriction	Several	(10, 11)
Alpha-interferon	Unknown	5	(13, 14)
Amphetamines	Sympathomimetic vasoconstriction	4	(15–17)
Digitalis	Mesenteric vasoconstrictor with toxic levels*	Numerous	(18)
Dopamine	Potent vasoconstrictor	Contributing factor	(19)
Epinephrine or norepinephrine	Potent vasoconstrictors	Contributing factors	(21)
Methysergide	Mesenteric vascular compression from retroperitoneal fibrosis	2	(22)
Nonsteroidal antiinflammatory drugs	Decreased synthesis of local vasodilatory prostaglandins	Several	(23, 24)
Pseudoephedrine	Alpha-adrenergic vasoconstrictor	6	(25, 26)
Vasopressin	Vasospasm	2	(27)
Barbiturates	Hypotension and hypoxemia with toxic dose	1	(28)
Chlorpromazine	May decrease colonic perfusion	2	(29)
Cyclosporine	Unknown	1	(30)
Danazol	Ischemia from constipation and bowel dilation	1	(31)
Diuretics	Contributes to nonocclusive mesenteric ischemia due to volume depletion	3	(32)
Flutamide	Unknown	1	(33)
Glycerin enema	Local vasospasm	2	(36)
Phosphosoda solution	Local vasospasm due to local hyperkalemia	2	(34)
Tricyclic antidepressants	May decrease colonic perfusion	3	(35)

*Association with ischemia primarily due to digitalis administration in cardiac failure and atrial fibrillation, conditions associated with colonic ischemia.

ESTROGENS AND PROGESTERONES. High-dose estrogens and progesterones in oral contraceptives produce a hypercoagulable state. Numerous cases of ischemic colitis have been associated with estrogen therapy due to mesenteric vein thrombosis (1, 7). The rectosigmoid and splenic flexure are most commonly involved. Symptoms and endoscopic findings generally resolve after cessation of therapy (1).

SODIUM POLYSTYRENE (KAYEXALATE) IN SORBITOL. Sodium polystyrene in sorbitol is commonly administered orally or rectally as a cation exchange resin to treat severe hyperkalemia. More than 25 patients have developed colonic ischemia after receiving this therapy (8). In one study, 2 of 117 postoperative patients receiving this therapy developed colonic necrosis (9). Pathologic examination reveals luminal kayexalate crystals adjacent to areas of mucosal necrosis. This finding implicates the kayexalate in causing the colonic ischemia. Many patients developing colonic ischemia with kayexalate therapy are, however, critically ill with uremia and have other risk factors for colonic ischemia. The colonic ischemia has been attributed to the hypertonicity of sorbitol or rapid mucosal shifts in electrolyte concentrations induced by kayexalate.

Probable Associations

ALOSETRON. Alosetron, a selective serotonin (5-hydroxytryptamine-3, 5-HT₃) antagonist, is effective in treating diarrhea-predominant irritable bowel syndrome in females. Ischemic colitis has been reported in association with alosetron therapy (10). Additionally, the Food and Drug Administration as of November 2000 received 49 reports of ischemic colitis during postmarket monitoring of adverse reactions to alosetron (11). The risk of ischemic colitis is estimated at 1 in 350 during alosetron therapy. Postulated mechanisms for this colonic ischemia include vasoconstriction due to 5-HT₁ or 5-HT₂ stimulation, particularly in patients with vascular endothelium damaged from hypertension or diabetes, and mucosal hypoperfusion due to increased intraluminal pressure from constipation and fecal impaction (12). Alosetron was removed from the regular prescription market because of this risk.

ALPHA-INTERFERON. Five cases of ischemic colitis have been associated with alpha-interferon therapy (13, 14). The mechanism of this proposed association is unknown.

AMPHETAMINES. Dextroamphetamine and methamphetamine are central nervous system stimulants used to treat narcolepsy and attention deficit disorders. These sympathomimetic vasoconstrictors have been associated with four cases of ischemic colitis (15–17).

DIGITALIS. Digitalis causes mesenteric vasoconstriction. Numerous reports have associated digitalis with intestinal ischemia. Patients typically have toxic serum digitalis levels

(18). This association is probably mostly due to administration of digitalis to treat cardiac failure and atrial fibrillation, conditions strongly associated with intestinal ischemia.

DOPAMINE. Dopamine is used to maintain the blood pressure in patients in shock. Hypotensive patients are at increased risk of developing nonocclusive mesenteric ischemia. Dopamine can exacerbate intestinal ischemia in hypotensive patients due to potent vasoconstriction (19). Dopamine should be carefully administered to maintain blood pressure in patients in shock, and is contraindicated in patients with suspected mesenteric ischemia.

EPINEPHRINE AND NOREPINEPHRINE. The catecholamines, epinephrine and norepinephrine, cause intense vasoconstriction and can thereby promote intestinal ischemia (20, 21). These drugs are, therefore, relatively contraindicated in patients at high risk for intestinal ischemia.

METHYSERGIDE. Methysergide, an ergot derivative and serotonin antagonist used to treat migraine headaches, occasionally causes retroperitoneal fibrosis. Two patients developed bowel infarction as a result of mesenteric vascular compression from methysergide-induced retroperitoneal fibrosis (22). Computerized tomography may demonstrate a retroperitoneal mass and hydronephrosis.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDS). NSAIDs are commonly prescribed anti-inflammatory and antipyretic medications used to treat arthritis and other musculoskeletal disorders. Several cases of ischemic colitis have been associated with nonselective NSAIDs (23). The mechanism may be decreased synthesis of local vasodilatory prostaglandins. Preferential COX-2 inhibitors, such as meloxicam, lose their COX-2 selectivity at high doses, and might also cause this toxicity at high doses (24).

PSEUDOEPHEDRINE. Pseudoephedrine is used as a nasal decongestant because it produces vasoconstriction due to an alpha-adrenergic action. Six cases of colonic ischemia have been associated with this medication (25, 26). The proposed mechanism is vasoconstriction.

VASOPRESSIN. Vasopressin is used to stem esophageal variceal bleeding because it reduces splanchnic perfusion due to vasospasm. Two cirrhotic patients developed ischemic colitis after intravenous therapy with vasopressin or a vasopressin analogue due to decreased splanchnic perfusion (27).

OTHER ASSOCIATIONS. Other reported associations include barbiturates (28), chlorpromazine (29), cyclosporine (30), danazol (31), diuretics (32), flutamide (33), phosphosoda bowel preparation (34), and tricyclic antidepressants

(35). Two cases of ischemic colitis have been attributed to local inferior mesenteric vasospasm following glycerin enema administration (36).

COLONIC PSEUDO-OBSTRUCTION

Before attributing colonic pseudo-obstruction to a medication (Table 2), it is imperative to exclude mechanical obstruction, as well as other causes of pseudo-obstruction, including hypothyroidism, enteric neuropathies, visceral myopathies, colonic ischemia, scleroderma or other collagen vascular diseases, infiltrative colonic diseases, abdominal radiotherapy, abdominal surgery, serum electrolyte abnormalities, parkinsonism, renal failure, and paraneoplastic effects. Mechanisms of drug-induced pseudo-obstruction include antagonism of prokinetic neurotransmitters (*e.g.*, phenothiazines), stimulation of antikinetic neurotransmitters (*e.g.*, clonidine), producing dysmotility (*e.g.*, ipecac), stimulating direct smooth muscle relaxation (*e.g.*, verapamil), and enteric nerve toxicity (*e.g.*, vincristine). Common clinical findings with medication-induced pseudo-obstruction include constipation, abdominal pain, abdominal distention, emesis, pyrexia, abdominal tenderness, abdominal tympany, and hypoactive bowel sounds. Patients may develop leukocytosis, particularly with severe colonic dilatation. Abdominal roentgenogram typically reveals diffusely dilated intestinal loops containing multiple air-fluid levels. Barium enema and colonoscopy do not reveal a mechanical cause of colonic obstruction. Therapy includes medication cessation, correction of electrolyte abnormalities, intravenous hydration, parenteral nutrition, enteric decompression with a nasogastric

tube, and careful monitoring of abdominal signs for decompensation requiring surgery. Colonoscopy may aid in colonic decompression.

Well-Established Associations

NARCOTICS. Loperamide, a predominantly peripheral opioid agonist, is used to control diarrhea because it inhibits gastrointestinal peristalsis. Loperamide, as well as other narcotics, can rarely cause colonic pseudo-obstruction due to this antikinetic effect (37, 38). This pseudo-obstruction usually responds to medication withdrawal, but can result in fulminant enterocolitis (39).

In the narcotic bowel syndrome, patients chronically administered narcotics for abdominal pain may paradoxically develop increased abdominal pain. The abdominal pain is typically chronic, diffuse, and colicky. Other clinical findings include constipation, abdominal distention, abdominal tenderness, and hypoactive bowel sounds. Abdominal roentgenograms show dilated loops of bowel and air-fluid levels, findings consistent with pseudo-obstruction. These gastrointestinal symptoms are partly attributed to narcotic tachyphylaxis and withdrawal, and partly attributed to opiate-induced hypoperistalsis and abdominal distention (40–42). An underlying psychiatric disorder may also contribute to the symptoms. Opiates must be discontinued. Clonidine has been used to treat this syndrome (40).

PHENOTHIAZINES. Phenothiazines are used to treat psychoses, nausea, and vertigo. Phenothiazines are cholinergic and serotonergic antagonists that inhibit gastrointestinal motility. More than 30 patients chronically receiving

Table 2. Medications Causing Colonic Pseudo-Obstruction

Medication	Proposed Mechanism	No. of Cases Reported	References
Well-established associations			
Loperamide	Inhibits motility	>5	(37–39)
Narcotics	Inhibits motility	Numerous	(40–42)
Phenothiazines	Inhibits motility due to cholinergic and serotonergic antagonism	>10	(43, 44)
Vincristine	Inhibits motility due to enteric neurotoxicity	10	(45, 46)
Probable associations			
Atropine (and other anticholinergics)	Inhibits motility due to parasympatholysis	3	(47)
Ganglionic blocking agents (<i>e.g.</i> , pentolium)	Inhibits motility due to parasympatholysis	7	(48)
Nifedipene	Direct smooth muscle relaxant	4	(38, 49)
Procainamide	Inhibits motility due to cholinergic antagonism	1	(50)
Tricyclic antidepressants	Inhibits motility due to cholinergic antagonism	14	(51, 52)
Amphetamines	Disordered motility due to sympathomimetic effects?	1	(53)
Barbiturates	Inhibits motility	1	(54)
Clonidine	Inhibits motility due to alpha 2-adrenergic stimulation	2	(55)
Dicumarol	Intramural hemorrhage causing bowel obstruction or enteric nerve injury?	6	(56)
Ipecac	Disordered motility due to emetine component	1	(57)
Verapamil	Calcium channel antagonist, smooth muscle relaxant	1	(58)

various phenothiazines developed pseudo-obstruction (43). In a review of 48 patients with colonic pseudo-obstruction, 42% were taking phenothiazines (44). Effects of phenothiazines are partly reversed by physostigmine, an anticholinesterase. Complications of this pseudo-obstruction include colonic perforation, necrotizing enterocolitis, and colonic ischemia.

VINCRIStINE. Vincristine is used in chemotherapy for leukemias and other malignancies. It inhibits gastrointestinal motility due to enteric neurotoxicity (45). About 10 patients have developed pseudo-obstruction attributed to vincristine (46). This effect is usually reversible.

Probable Associations

ATROPINE AND RELATED ANTICHOLINERGIC MEDICATIONS. Atropine, benzotropine mesylate (cogentin), and ipratropium bromide are antimuscarinic alkaloids used for cardiopulmonary resuscitation, lower urinary tract dysmotility, irritable bowel syndrome, and parkinsonism. Three patients developed pseudo-obstruction associated with these medications (47). These medications may have contributed to the pseudo-obstruction due to their parasympatholytic effects.

GANGLIONIC BLOCKING AGENTS. Pentolinium tartrate, hexamethonium, and mecamlamine are ganglionic blocking agents once used to treat severe hypertension. At least seven patients developed pseudo-obstruction believed due to parasympatholysis induced by these ganglionic blocking agents (48).

NIFEDIPINE. Four patients developed colonic pseudo-obstruction associated with nifedipine therapy (38, 49). Nifedipine, a calcium channel blocker, decreases intestinal motility by directly relaxing smooth muscle.

PROCAINAMIDE. One patient developed colonic pseudo-obstruction associated with procainamide therapy (50). The pseudo-obstruction was attributed to the anticholinergic effects of procainamide.

TRICYCLIC ANTIDEPRESSANTS. Tricyclic antidepressants, used to treat affective disorders, have anticholinergic effects and can cause constipation. Fifteen cases of pseudo-obstruction have been associated with tricyclic antidepressants, including amitriptyline, nortriptyline, imipramine, and doxepin (51, 52). Treatment includes physostigmine administration.

OTHER ASSOCIATIONS. Other reported associations include amphetamines (53), barbiturates (54), clonidine (55), dicumarol (56), ipecac (57), and verapamil (58).

INFECTIOUS OR NECROTIZING ENTEROCOLITIS

Medications may promote enteric infections by altering the normal bowel flora (e.g., pseudomembranous colitis from antibiotic therapy), decreasing immunologic defense against infections (e.g., neutropenic colitis from chemotherapy), promoting microorganism virulence (e.g., *Yersinia enterocolitica* infection with deferoxamine therapy), injuring mucosa (e.g., necrotizing enterocolitis from hyperosmolar formulas), or promoting bacterial overgrowth due to drug-induced hypoperistalsis (e.g., loperamide) (Table 3).

Well-Established Associations

ANTIBIOTICS. Pseudomembranous colitis is frequently induced by antibiotics, because *Clostridium difficile* proliferates in the gastrointestinal tract when the normal enteric flora is altered by antibiotics. The most commonly involved antibiotics are ampicillin, amoxicillin, penicillin, clindamycin, cephalosporins, and trimethoprim-sulfamethoxazole (59). Clinical findings include diarrhea, pyrexia, abdominal pain, abdominal tenderness, and leukocytosis. The diagnosis is made by demonstration at colonoscopy of yellowish plaques of pseudomembranes covering the colonic mucosa or by detection of *C. difficile* toxin in the stool. Pseudomembranous colitis mandates discontinuing the offending antibiotic. Therapy for moderate or severe disease includes oral vancomycin, metronidazole, or cholestyramine (1).

AMPICILLIN, AMOXICILLIN, AND ERYTHROMYCIN. Ampicillin, amoxicillin, and erythromycin are associated with a hemorrhagic colitis that differs from pseudomembranous colitis in that the patients have neither pseudomembranes in the colon nor the toxin of *C. difficile* in the stool (60). Patients typically present with bloody diarrhea and abdominal cramps, and have a predominantly right-sided colitis (60, 61). Patients usually rapidly improve after antibiotic cessation. The mechanism is believed to be overgrowth of a pathogen different than *C. difficile*, possibly *Klebsiella oxytoca* (62).

CHEMOTHERAPY. Patients receiving chemotherapy, including cytosine arabinoside, cytarabine, cisplatin, fluorouracil, vincristine, adriamycin, 5-fluorouracil, thioguanine, and mercaptopurine, are at risk of developing necrotizing enterocolitis or neutropenic colitis (63, 64). When the cecum is predominantly affected, the syndrome is called neutropenic typhlitis. The common feature in all cases is profound drug-induced leukopenia and neutropenia (<100 neutrophils/mm³) that permits mural bacterial invasion. Risk factors for this colitis include underlying leukemia and administration of drugs toxic to gastrointestinal mucosa, such as cytosine arabinoside. Clinical findings include abdominal pain, diarrhea, abdominal tenderness, abdominal distention, rebound tenderness, abdominal guarding, pyrexia, stomatitis, and fecal occult blood (65). Radiologic findings include dilated loops of bowel, air-fluid levels, mural thumbprinting, and pneumatosis

Table 3. Medications Causing Infectious or Necrotizing Enterocolitis

Medication	Toxicity	Proposed Mechanism	No. of Cases Reported	References
Well-established associations				
Antibiotics	Pseudomembranous colitis	Enterotoxin produced by <i>Clostridium difficile</i> due to altered enteric flora	Many	(59)
Ampicillin, amoxicillin, & erythromycin	Hemorrhagic colitis	Overgrowth of a bacterial pathogen due to altered enteric flora	Numerous	(60, 61)
Chemotherapy	Neutropenic colitis	Bacterial mural invasion due to severe neutropenia	Numerous	(63–65)
Corticosteroids	Malakoplakia	Defective macrophagic phagocytosis due to immunosuppression	Numerous	(66, 67)
Deferoxamine	Yersinia enterocolitis	Acts as a siderophore which promotes Yersinia virulence	12	(68)
Hyperosmolar formulas	Necrotizing enterocolitis	Hypertonicity may alter enteric flora or injure colonic mucosa	Numerous	(69)
Probable associations				
Hyperosmolar medication formulations (e.g., vitamin E)	Necrotizing enterocolitis	Hyperosmolar preparation may alter enteric flora or injure colonic mucosa	Numerous	(71)
Loperamide	Necrotizing enterocolitis	Hypoperistalsis leads to bowel distention and ischemia	2	(70)
Chlorpropamide	Pseudomembranouscolitis	Sulfa moiety hypersensitivity or effects on normal enteric flora	1	(72)
Methylxanthines	Necrotizing enterocolitis	Bacterial overgrowth due to enteric hypoperistalsis?	5	(73, 74)
Mianserin	Neutropenic colitis	Neutropenia leads to bacterial mural invasion	1	(75)

coli (64). Pathologic examination of the colon reveals bacterial proliferation with an attenuated inflammatory response. Patients frequently have bacteremia. Therapy includes cessation of chemotherapy, fluid resuscitation, antibiotic therapy, and total parenteral nutrition. Recovery usually comes after normalization of the neutrophil count after chemotherapy discontinuation. Administration of granulocyte colony stimulation factor (G-CSF) is recommended because this therapy significantly shortens the duration of neutropenia, pyrexia, and hospitalization. Complications include intestinal hemorrhage, necrosis, perforation, peritonitis, and shock (64). This condition can be fatal. One patient developed acute hemorrhagic colitis without neutropenia, attributed to cyclophosphamide administration. Chemotherapy may also be a risk factor for severe pseudomembranous colitis.

CORTICOSTEROIDS. Patients immunosuppressed by corticosteroids are at increased risk of developing malakoplakia, possibly due to defective macrophagic phagocytosis from immunosuppression (66, 67). Colonic involvement can cause diarrhea, abdominal pain, and rectal bleeding. The typical colonoscopic lesions are small, yellowish, and soft plaques. Patients can, however, develop colonic obstruction from a colonic mass or stricture due to malakoplakia. Histologic examination of colonic biopsies reveals a granulomatous infiltrate with histiocytes containing an eosinophilic granular cytoplasm (von Hansemann cells) and characteristic basophilic cytoplasmic spherules (Michaelis-Guttman bodies).

DEFEROXAMINE. Deferoxamine is used to treat iron or aluminum overload due to its ability to chelate iron or aluminum. Deferoxamine acts as a siderophore that promotes Yersinia replication. About a dozen cases of severe Yersinia enterocolitis have been associated with deferoxamine (68). Clinical findings include vomiting, abdominal pain, diarrhea, bloody stools, pyrexia, and a palpable right lower quadrant mass. Abdominal computerized tomography may show right lower quadrant bowel wall thickening and mesenteric lymphadenopathy. Gross pathologic findings include a fibrinopurulent indurated right lower quadrant mass, mesenteric lymphadenopathy, and mucosal ulceration. The terminal ileum, appendix, or cecum may be affected. Complications include intestinal perforation, local abscess, and hepatosplenic infection (68). Treatment includes medication discontinuation and appropriate antibiotics.

HYPEROSMOLAR FORMULAS. Hyperosmolar formulas have been largely abandoned as feeding solutions in infants due to numerous reports of necrotizing enterocolitis (69). Risk factors include severe prematurity and concomitant milk feedings. Oral nystatin or vitamin E administered in hypertonic solutions have also been associated with necrotizing enterocolitis. Pathophysiologic mechanisms may include enteric mucosal injury due to osmotic flows, mucosal vascular redistribution, and altered enteric flora. Clinical findings include pyrexia, abdominal pain, abdominal distention, abdominal tenderness, and bloody stools. Roentgenographic

findings include pneumatosis coli, portal venous gas, mural thumbprinting, ulceration, and ascites. Treatment includes cessation of hyperosmolar solutions, total parenteral alimentation, broad-spectrum antibiotics, and sometimes bowel resection.

Probable Associations

LOPERAMIDE. Four cases of necrotizing enterocolitis in infants were associated with loperamide (70). Loperamide may promote bacterial overgrowth by inhibiting intestinal motility. Patients present with pyrexia, abdominal distention, dehydration, hypoactive bowel sounds, and bloody stools. Roentgenographic findings include dilated bowel loops, pneumatosis coli, and multiple air-fluid levels. Both patients required surgery to remove gangrenous ileocolonic bowel.

VITAMIN E. Vitamin E is used pharmacologically to treat retrolental fibroplasia. In a large retrospective study, 16% of premature infants receiving oral vitamin E developed necrotizing enterocolitis (71). Oral vitamin E administration must be discontinued. About one-third of infants with this enterocolitis required surgery. The risk of enterocolitis is reduced by parenteral administration of vitamin E.

OTHER ASSOCIATIONS. One case of pseudomembranous colitis was associated with chlorpropamide therapy (72). Methylxanthines have been associated with necrotizing enterocolitis (73, 74). One patient developed neutropenic colitis after administration of mianserin, an antidepressant (75). The clinical presentation, natural history, and underlying pathophysiology are similar to that described for neutropenic colitis from chemotherapy.

INFLAMMATORY, CYTOTOXIC, OR ALLERGIC COLITIS

Medications may produce a toxic colitis due to direct drug mucosal cytotoxicity (*e.g.*, chrysotherapy), antimetabolite effects that selectively affect rapidly dividing intestinal enterocytes (*e.g.*, methotrexate), or local drug overdose due to excessive local release (*e.g.*, enteric coated potassium chloride) (Table 4). Medications may produce colitis due to drug allergy or hypersensitivity (*e.g.*, alpha methyl dopa), or stimulation of selected local inflammatory cells including eosinophils (*e.g.*, carbamazepine), and macrophages (*e.g.*, ipecac).

Well-Established Associations

GOLD COMPOUNDS. Chrysotherapy, for rheumatoid arthritis and other collagen vascular diseases, commonly causes diarrhea. More than 30 cases of enterocolitis have

Table 4. Medications Causing an Allergic, Cytotoxic, or Inflammatory Colitis

Medication	Proposed Mechanism	No. of Cases Reported	References
Well-established associations			
Gold compounds	Direct colonic mucosal toxin <i>versus</i> hypersensitivity	>30	(76, 77)
Nonsteroidal antiinflammatory drugs	Decreased prostaglandin synthesis due to cyclooxygenase inhibition	Numerous	(78–80)
Potassium chloride	Local potassium release causes local mucosal vasospasm and ischemia	Numerous	(81)
Probable associations			
Alpha-methyl dopa	Drug allergy	7	(82, 83)
Bisacodyl	Causes mild mucosal inflammation	Several	(84)
Flucytosine	5-Fluorouracil injures rapidly dividing cells including enterocytes	5	(85, 86)
Methotrexate	Injures rapidly dividing cells, including enterocytes, due to folic acid inhibition	4	(87)
Salicylates	Hypersensitivity	5	(88, 89)
Selective COX-2 inhibitors	Inhibition of cyclo-oxygenase activity	3	(91, 92)
Sodium phosphate solution	Increased colonocyte turnover?	Numerous	(93)
Sulfasalazine	Salicylate moiety hypersensitivity	7	(94)
Alpha-interferon	Induces a hemorrhagic colitis due to immunomodulation?	1	(95, 96)
Carbamazepine	Eosinophilic mucosal inflammation	1	(97)
Cimetidine	Hypersensitivity?	1	(98)
Ipecac	Pigment accumulation in mucosal macrophages	1	(99)
Isoretinoin	Unknown	1	(100)
Mephenamic acid	Unknown	1	(101)
Penicillamine	Unknown	1	(102)
Rifampin	Unknown	1	(103)
Simvastatin	Unknown	1	(104)
Trientine	Unknown	2	(105)

COX—cyclo-oxygenase.

been associated with chrysotherapy, possibly due to a hypersensitivity reaction (76). The onset of the enterocolitis may be delayed up to 3 months after instituting therapy. Clinical findings include watery diarrhea, bloody stools, emesis, abdominal pain, pyrexia, abdominal tenderness, rash, leukocytosis, anemia, eosinophilia, and hypoproteinemia (77). Colonoscopy reveals friable, edematous, erythematous, and ulcerated colonic mucosa. Pathologic examination of colonic biopsies reveals mucosal hemorrhage, ulceration, and inflammatory infiltration, occasionally with eosinophils (1). The colitis may be fatal (1). Chrysotherapy must be discontinued. Proposed therapies include steroids, antibiotics, disodium cromoglycate, and chelating agents.

NSAIDS. Numerous orally administered NSAIDs, such as ibuprofen, meclufenamate, diclofenac sodium (voltage), mefenamic acid, and naproxen, have been sporadically associated with colitis (78). Indeed, in one large case-control study 74% of patients with new onset colitis were recently exposed to NSAIDs or salicylates *versus* 30% of in-patient controls (79). This difference was statistically significant (odds ratio = 6.2, $p < 0.001$). Administration by suppositories has also been associated with proctitis (78). NSAIDs also can exacerbate preexisting ulcerative colitis (78). NSAIDs may induce colitis by inhibiting cyclooxygenase and decreasing prostaglandin synthesis; prostaglandins are cytoprotective in the intestine (78). Clinical findings include abdominal pain, pyrexia, bloody stools, anorexia, involuntary weight loss, abdominal tenderness, an elevated erythrocyte sedimentation rate, hypoalbuminemia, and anemia. Colonoscopy may reveal mucosal erosions, aphthae, and ulcers (80). Pathologic examination of colonic biopsies usually reveals inflammatory infiltration. Patients usually respond well to medication withdrawal, but occasionally require emergency surgery for colonic perforation (78). Steroids may be used for severe colitis (78).

NSAIDs increase the risk of spontaneous colonic perforation at colonic diverticula or other colonic sites. NSAIDs have been associated with diaphragm-like strictures in the small or large intestine.

POTASSIUM CHLORIDE. Potassium chloride administered in enteric-coated tablets used to be an important cause of intestinal ulcers. The frequency of this toxicity has decreased with discontinuance of enteric-coated potassium chloride, but this toxicity can rarely occur with potassium chloride packaged in wax matrices due to local release and intestinal absorption of high concentrations of potassium, leading to local vasospasm and ischemia (81). Ulcerations frequently occur at sites of preexisting luminal narrowing, because of prolonged exposure at these sites. Patients present with gastrointestinal bleeding, perforation, or obstruction. Roentgenography may demonstrate intestinal obstruction, but rarely delineates the ulcers.

Probable Associations

ALPHA-METHYLDOPA. Eight cases of acute colitis have been reported with alpha-methyldopa, an antihypertensive medication structurally related to catecholamines (82, 83). Clinical findings include watery or bloody diarrhea, malaise, pyrexia, a macular rash, hepatomegaly, leukocytosis, and fecal leukocytes. Sigmoidoscopy may reveal hyperemic friable mucosa, and petechiae. In all cases, medication cessation led to rapid improvement. Rechallenge in four cases led to the redevelopment of symptoms. The hypothesized mechanism is a drug allergy.

BISACODYL. Bisacodyl enema causes acute colonic mucosal injury (84). The injury is characterized by superficial mucosal inflammation with a predominantly neutrophilic infiltrate and flattening of the surface epithelium (84). The injury is typically transient and mild.

FLUCYTOSINE. Flucytosine is used to treat cryptococcosis and other fungal infections. Five patients developed severe intestinal injury associated with flucytosine possibly due to local toxic effects on protein synthesis (85, 86). Clinical findings include abdominal pain, pyrexia, diarrhea, and abdominal distention. Barium studies may reveal luminal narrowing or mucosal ulceration. Colonoscopy may reveal mucosal erythema and edema. Three patients developed intestinal perforation. This toxicity may be due to intestinal conversion of flucytosine into 5-fluorouracil, an antimetabolite.

METHOTREXATE. Methotrexate is used to treat leukemias, rheumatic diseases, and psoriasis. Methotrexate impairs folic acid metabolism, blocks deoxyribonucleic acid synthesis, and arrests cell division. It is, therefore, cytotoxic to rapidly dividing gastrointestinal mucosal cells. Four patients developed colitis following methotrexate therapy (87). Clinical findings included pyrexia, diarrhea, hematochezia, emesis, anorexia, stomatitis, abdominal distention, abdominal tenderness, and hypoactive bowel sounds. Abdominal roentgenogram may reveal thumbprinting, mucosal irregularity, dilated intestinal loops, and air-fluid levels. Colonoscopy may reveal mucosal erythema, friability, ulcers, and mucopus. The primary therapy is medication discontinuation.

SALICYLATES. Five patients developed bloody diarrhea after salicylate administration (88). Postulated reasons for aspirin toxicity include a hypersensitivity reaction, increased intestinal permeability, or free-radical production (89). Clinical findings included abdominal pain, pyrexia, abdominal distention, emesis, a rash, anemia, eosinophilia, hypoalbuminemia, and an elevated erythrocyte sedimentation rate. Colonoscopic findings included mucosal ulcers, friability, and erythema. Pathologic examination of colonic biopsies revealed mucosal ulcers, crypt abscesses, and eosinophilic infiltration.

SELECTIVE CYCLO-OXYGENASE-2 (COX-2) INHIBITORS. Selective COX-2 inhibitors theoretically block the inflammatory response mediated by COX-2 without inhibiting COX-1, which is necessary for gastrointestinal homeostasis (90). Selective COX-2 inhibitors appear to significantly decrease but not eliminate the gastrointestinal toxicity associated with nonselective NSAIDs. Selective COX-2 inhibitors have been associated with several cases of mild self-limited colitis, hemorrhagic colitis, and ischemic colitis (91, 92).

SODIUM PHOSPHATE SOLUTION. Oral sodium phosphate solution has been associated with acute transient focal colitis. The characteristic lesion is colonic aphthous ulceration. The incidence of this toxicity was 2.6% in a series of 687 consecutive patients (93).

SULFASALAZINE. Sulfasalazine, a therapy for inflammatory bowel disease, was reported to paradoxically reactivate quiescent ulcerative colitis in seven patients (94). Clinical findings included emesis, headache, abdominal pain, pyrexia, bloody diarrhea, iridocyclitis, rash, arthralgias, leukocytosis, eosinophilia, anemia, hypoalbuminemia, and an elevated erythrocyte sedimentation rate. Sigmoidoscopy may reveal diffuse hyperemia, granularity, friability, hemorrhage, and exudates. Pathologic examination of colonic biopsies reveals mucosal inflammation, crypt abscesses, and goblet cell depletion. In all cases, the symptoms resolved after medication discontinuance and recurred with medication rechallenge. The mechanism of this toxicity may be an allergy to the salicylate moiety. Other etiologies must be excluded before attributing a flare of ulcerative colitis to sulfasalazine.

OTHER ASSOCIATIONS. Other reported associations include alpha-interferon (95, 96), carbamazepine (97), cimetidine (98), ipecac (99), isotretinoin (100), mephenamic acid (101), penicillamine (102), rifampin (103), simvastatin (104), and trientine (105).

LYMPHOCYTIC OR COLLAGENOUS COLITIS

Patients with lymphocytic or collagenous colitis present with chronic watery and nonbloody diarrhea. Less common symptoms include abdominal pain and involuntary weight loss. Colonoscopy typically reveals no abnormalities, or minimal and nonspecific abnormalities, such as erythema or edema, in either condition (106). Pathologic examination of colonic biopsies, taken from endoscopically normal-appearing colon, reveals a thickened basement membrane in collagenous colitis caused by collagen deposition, and intraepithelial lymphocytic and other mononuclear cell infiltration. Lymphocytic colitis is a closely related but milder condition, in which the inflammatory infiltrate is present without a thickened base-

ment membrane (106). In both colitides the crypt architecture is preserved.

Well-Established Associations

NSAIDS. An association of NSAIDs with collagenous colitis has been reported in several case reports, as well as in several case-control studies (107, 108) (Table 5). Symptoms include abdominal pain, watery nonbloody diarrhea, mucoid rectal discharge, abdominal distention, flatulence, and involuntary weight loss. Colonoscopy and barium enema are generally within normal limits. Clinical response to sulfasalazine or corticosteroids is variable.

Probable Associations

CYCLO 3 FORT. Cyclo 3 Fort, a combination of hesperidine methylchalcone, ascorbic acid, and a vegetable extract, has been used in France for symptomatic relief of venous insufficiency (109). Eight cases of lymphocytic colitis have been associated with this agent, possibly due to immune activation (109–111).

FLUTAMIDE. At least five cases of lymphocytic or collagenous colitis have been associated with flutamide (112, 113).

LANSOPRAZOLE. Lansoprazole is a proton pump inhibitor used to treat or prevent peptic ulcers, reflux esophagitis, and stress ulcers. Lansoprazole causes diarrhea in about 5% of cases (114). At least seven cases of lymphocytic colitis and two cases of collagenous colitis have been associated with lansoprazole therapy (114, 115).

RANITIDINE. Ranitidine has been associated with at least three cases of lymphocytic colitis (116). The postulated mechanism is colonic immune activation by ranitidine (117).

SALICYLATES. Salicylates have been rarely associated with collagenous colitis (118). In one reported case the diarrhea ceased and the histologic abnormalities reversed soon after discontinuing salicylate therapy (118).

TICLOPIDINE. Ticlopidine is an antiplatelet agent used for cardiovascular prophylaxis. At least 11 cases of lymphocytic or collagenous colitis have been associated with ticlopidine (119, 120). Patients typically present with unexplained chronic diarrhea that commences after beginning ticlopidine therapy.

OTHER ASSOCIATIONS. Lymphocytic colitis has also been associated with acarbose (121, 122), bentazepam (113), tardyferon (123), and vinburnine (124).

Table 5. Medications Causing Lymphocytic or Collagenous Colitis

Medication	Proposed Mechanism	No. of Cases Reported	References
Well-established associations			
Nonsteroidal antiinflammatory drugs	Decreased intestinal cytoprotection and immunologic defense due to loss of prostaglandins	Numerous	(107, 108)
Probable associations			
Cyclo 3 fort	Lymphocytic colitis due to immunologic activation	6	(109–111)
Flutamide	Lymphocytic colitis due to immunologic activation?	5	(112, 113)
Lansoprazole	Lymphocytic or collagenous colitis due to immunologic activation	9	(114, 115)
Ranitidine	Lymphocytic colitis due to immunologic activation	3	(116, 117)
Salicylates	Decreased intestinal cytoprotection and immunologic defense due to loss of prostaglandins	Several	(118)
Ticlopidine	Lymphocytic colitis due to immunologic activation?	11	(119, 120)
Acarbose	Intestinal glucosidase inhibition increases intestinal starch, butyrate, and prostoglandin production?	1	(121, 122)
Benzazepam	Lymphocytic colitis due to immune activation?	1	(113)
Tardyferon	Lymphocytic colitis due to immunologic activation?	1	(123)
Vinburnine	Lymphocytic colitis due to immunologic activation?	1	(124)

CATHARTIC COLON AND COLONIC OBSTRUCTION

Well-Established Associations

CATHARTICS. Chronic use of stimulant cathartics, such as anthraquinones and castor oil, can cause the cathartic colon (Table 6). Symptoms include diarrhea, lassitude, abdominal pain, abdominal distention, and involuntary weight loss (125). Many affected patients have psychiatric disturbances. Common laboratory abnormalities are hypokalemia, prerenal azotemia, and hypocalcemia. Radiographic abnormalities of cathartic colon include colonic dilation, foreshortening, hypomotility, loss of haustrae, colonic spasm, and a patulous ileocecal valve. Histologic examination of the colon demonstrates a thin bowel wall, atrophic mucosa, and axonal degeneration within enteric nerves. The proposed mechanism is injury to the myenteric plexus.

Chronic use of anthraquinone cathartics, such as cascara sagrada, senna, rhubarb, and aloes, can produce melanosis coli. Colonoscopy reveals intense black mucosal pigmentation with a pink reticular border. Histologic examination re-

veals pigment deposition within mucosal macrophages (126), possibly due to increased uptake of degenerating cell components following medication-induced apoptosis of colonocytes (127). The pigmentation may be due to lipofuscin. The primary therapy of cathartic colon or melanosis coli is medication discontinuation.

METHYSERGIDE. Two patients developed a rectosigmoid stricture from external compression by methysergide-induced retroperitoneal fibrosis (128). Clinical findings included constipation, abdominal pain, abdominal distention, pyrexia, and leukocytosis. Therapy includes medication discontinuation and colonic surgery.

NONMEDICINAL TOXINS: RECTAL ADMINISTRATION

Colitis has been reported due to herbal medications, illicit drugs, contrast materials, detergents, and corrosive

Table 6. Medications Causing Cathartic Colon and Colonic Obstruction

Medicine	Colonic Toxicity	Proposed Mechanism	No. of Cases Reported	References
Well-established associations				
Anthraquinone cathartics	Melanosis coli	Lipofuscin accumulates in mucosal macrophages	Numerous	(126, 127)
Stimulant cathartics	Cathartic colon	Neuromuscular damage	Numerous	(125)
Methysergide	Colonic obstruction	Extrinsic colonic compression due to retroperitoneal fibrosis	2	(128)

Table 7. Colonic Toxicity of Rectally or Orally Administered Nonmedicinal Compounds

Compound	Mechanism	No. of Cases Reported	References
Rectal administration: Well-established or probable associations			
Acetic acid	Corrosive	1	(130)
Barium	Highly viscous barium can impede colonic emptying and promote fecal impaction	Numerous	(131, 132)
Chloro-m-xyleneol (Dettol)	Direct toxin at high concentration	1	(130)
Detergent enemas	Caustic at high concentration	7	(133–135)
Ethyl alcohol	Direct toxin at high concentration	1	(136)
Formalin	Direct toxin (causes crosslinking of mucosal proteins)	1	(137)
Herbal remedies	Various toxins	5	(130)
Hydrofluoric acid	Caustic acid	1	(129)
Hydrogen peroxide	Explosive intracellular oxygen release	34	(138, 139)
Glutaraldehyde	Direct toxin (causes crosslinking of mucosal proteins)	1	(140, 141)
India ink	Noxious impurities in India ink injected into colonic wall during tattooing	Several	(142, 143)
Potassium permanganate	Corrosive oxidizing agent	1	(130)
Radiographic contrast	Hypertonic solutions in obstructed colon	>5	(144)
Sodium hydroxide	Corrosive base	1	(145)
Oral administration: Probable associations			
<i>Amanita phalloides</i>	Pseudo-obstruction (enteric toxin)	3	(148)
Ethyl alcohol	Pseudo-obstruction (metabolic acidosis)	2	(149)
Paraquat	Pseudomembranous colitis?	1	(150)
Seirogan	Toxic phenol levels with overdose	1	(147)

substances that are administered intrarectally by suppository, enema, or colonoscopic fluid instillation (129) (Table 7). Toxic exposure may result from conventional medical therapy, herbal or other unconventional medical therapy, radiographic examination, colonoscopic examination, deliberate self-mutilation, or accidental exposure. Mechanisms include mucosal toxicity from corrosive acids (*e.g.*, hydrofluoric acid), bases (sodium hydroxide), or other caustic agents (*e.g.*, potassium permanganate); intracellular explosive oxygen production (*e.g.*, hydrogen peroxide); osmotic flows due to agent hypertonicity (*e.g.*, radiographic contrast agents); and cross-linking of extracellular and intracellular proteins (*e.g.*, formalin). Clues that a colitis may be due to an intrarectally administered agent include perianal excoriation, segmental distal colitis due to a concentration gradient from enema administration, membership in a high-risk group, such as schizophrenic patients, and recent diagnostic or therapeutic administration of high-risk solutions such as hypertonic contrast agents or detergent enemas (129).

Well-Established or Probable Associations

ACETIC ACID. Acetic acid is a corrosive liquid used in manufacturing drugs, plastics, and food additives. One patient developed bowel infarction after application of a concentrated acetic acid enema (130). Abdominal roentgenography revealed pneumoperitoneum.

BARIUM. Barium is a highly viscous contrast agent that is insoluble in water. Barium enemas are usually very safe, but

can rarely cause or promote fecal impaction (131). Affected patients nearly always have another risk factor for fecal impaction, such as neurologic bowel dysfunction, cystic fibrosis, or scleroderma (131, 132). Patients at high risk for fecal impaction should receive purgatives after barium enema.

CHLORO-M-XYLENOL. Chloro-m-xyleneol (Dettol), a household disinfectant, is a moderate tissue toxin. One patient presented with bloody diarrhea after application of a Dettol enema (130). Endoscopic findings included mucosal edema, granularity, and friability.

DETERGENT ENEMAS. Seven patients developed colitis from highly concentrated detergent enemas due to detergent effects on colonic mucosa (133, 134). Patients present with bloody diarrhea, abdominal pain, emesis, pyrexia, abdominal tenderness, abdominal distention, and leukocytosis. Barium enema may reveal colonic spasm, luminal narrowing, and irregular mucosa (135). Colonoscopic findings include friable, edematous, granular, and erythematous mucosa, coated by a serosanguinous exudate. Severe exposure can produce colonic necrosis or strictures. Abnormalities seen on barium enema months after exposure include a smooth, anastomotic, and foreshortened colon.

ETHYL ALCOHOL. One patient developed abdominal pain and hemochezia after administration of a highly concentrated ethyl alcohol enema due to direct mucosal

toxicity (136). Colonoscopic findings included mucosal erythema and ulceration.

FORMALIN. One patient experienced left lower quadrant abdominal pain and rectal bleeding after administration of a formalin enema (137). Colonoscopy revealed mucosal edema, erythema, and erosions. The symptoms and colonoscopic abnormalities gradually resolved after corticosteroid administration.

HERBAL MEDICINES. Five members of African tribes developed severe colitis from various toxins in herbal enemas (130). Clinical findings included rectal bleeding, pyrexia, abdominal pain, and perianal excoriation. Radiography may demonstrate colonic dilation proximal to a stricture. Pathologic examination of colonic biopsies may reveal hemorrhagic necrosis, inflammation, and ulceration.

HYDROFLUORIC ACID. Hydrofluoric acid is highly caustic. One patient developed bloody diarrhea from fulminant acute colitis after self-administering a hydrofluoric acid enema (129). Flexible sigmoidoscopy and a gastrografin (meglumine diatrizoate) enema revealed severe mucosal ulceration and edema in the rectum and sigmoid. The patient received calcium carbonate enemas to neutralize the rectal acid and to bind and detoxify the fluoride ion. Laparotomy revealed a necrotic, purulent sigmoid and intraperitoneal pus. The patient recovered after undergoing a sigmoid resection, but subsequently developed a colonic stricture.

HYDROGEN PEROXIDE. Thirty-four patients have developed colonic injury from hydrogen peroxide exposure (138). This compound penetrates intracellularly where it explosively releases oxygen (139). Exposure usually occurs when residual hydrogen peroxide is instilled during colonoscopy because of inadequate washing of colonoscopes after sterilization (138). Colonoscopic instillation instantaneously produces mucosal blanching and effervescence (snow-white sign) at colonoscopy (138). Clinical findings include bloody diarrhea, abdominal pain, pyrexia, tenesmus, and leukocytosis. Colonoscopic findings days after severe exposure include friability, granularity, stricture, ulceration, purulent exudation, and edema. Roentgenographic findings can include pneumatosis coli, ulceration, and pneumoperitoneum from colonic perforation.

GLUTARALDEHYDE. Like hydrogen peroxide, residual glutaraldehyde in a colonoscope or sigmoidoscope after sterilization can cause colitis. Numerous cases of this complication have been reported (140). This is preventable by thoroughly rinsing the colonoscope after disinfection with glutaraldehyde (141).

INDIA INK. Patients have rarely developed a colonic abscess or focal fat necrosis at the site where India ink had been injected to mark (tattoo) a site during colonoscopy (142, 143).

POTASSIUM PERMANGANATE. One patient developed bloody diarrhea after intrarectal application of potassium permanganate, a highly corrosive oxidizing agent (130). Endoscopic findings included mucosal friability and hemorrhage due to a hemorrhagic colitis.

RADIOGRAPHIC CONTRAST AGENTS. Hypertonic contrast agents administered by enema are generally very safe. However, at least five cases of colonic toxicity have been reported due to prolonged exposure to water-soluble contrast agents administered by enema, including sodium diatrizoate (hypoaque), meglumine (renografin-76), and gastrografin. Risk factors for prolonged exposure are colonic obstruction due to adenocarcinoma or meconium ileus. Clinical findings include pyrexia, abdominal pain, abdominal tenderness, and abdominal distention. Abdominal roentgenogram may demonstrate retained radiographic contrast in bowel, dilated bowel loops, mural thumbprinting, and mucosal ulcers. Colonoscopy may reveal mucosal friability and luminal dilation. Complications include perforation and peritonitis (144). The postulated mechanism is mucosal osmotic flow due to contrast agent hypertonicity, but the findings may be largely due to the underlying colonic obstruction.

SODIUM HYDROXIDE. Sodium hydroxide is a corrosive agent. One patient presented with abdominal pain, abdominal tenderness, rectal tenderness, rectal bleeding, pyrexia, and leukocytosis after exposure to a sodium hydroxide enema (145). Sigmoidoscopy revealed a purulent exudate, mucosal hemorrhage, ulcers, and luminal narrowing in the distal colon. Barium enema revealed a thickened wall, narrow lumen, and ulcerated mucosa in the rectum and sigmoid. Pathologic examination of the resected specimen revealed submucosal fibrosis and mucosal inflammation.

NONMEDICINAL COMPOUNDS: ORAL ADMINISTRATION

Probable Associations

SEIROGAN. Seirogan is used as an herbal therapy for diarrhea because wood creosote, its principal component, inhibits intestinal peristalsis (146). Seirogan, however, also contains a phenolic derivative. One patient developed a paralytic ileus after ingesting an overdose of seirogan due to toxic plasma phenol levels (147). This patient also presented with unconsciousness, dyspnea, and dark brown urine due to the phenol toxicity.

Other reported associations include pseudo-obstruction with the toxic mushroom *Amanita phalloides* (148), pseudo-obstruction with ethyl alcohol (149), and pseudomembranous colitis with paraquat, an herbicide (150) (Table 7).

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