NON STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

These are the most common drugs causing intestinal injury. In the majority of cases these agents are not physician prescribed but are obtained "over the counter" from drug stores and supermarkets etc. Their use is so widespread that patients may be assumed to be taking them until proved otherwise. Unfortunately, information about their use is seldom provided on patient pathology requisitions.

Advertisers’ claims that their NSAIDs are safer than the other companies NSAIDs may or may not be correct and it is safe to assume that any NSAID may cause GI problems. The pathologic findings do not differ among the various brands available. Low-dose preparations may also cause problems although as a general rule higher doses and prolonged periods of administration result in greater problems. It has been estimated that low-dose aspirin administration increases the risk of upper gastro-intestinal bleeding by 2-4%.

In the UK it has been estimated that there are 12,000 hospital admissions annually that are attributable to NSAID use. 2230 of these patients died.

**Mechanisms of action**: 1) Many NSAIDs are acidic in nature (e.g. aspirin) and are capable of directly interfering with the mucus that covers the gastrointestinal mucosa. This may lead to breaks in the mucous barrier. In addition, the chemical nature of the NSAIDs themselves can directly irritate the exposed mucosa. 2) Cyclooxygenase (COX) produces prostaglandins that are important for maintaining mucosal integrity in gastrointestinal mucosa, particularly in the stomach where they mediate blood flow and epithelial repair. NSAIDs inhibit COX1 and consequently prostaglandin production resulting in neutrophil mediated damage to mucosal endothelium and ulceration.

**Esophagus**: NSAID damage in the esophagus produces a syndrome known as "pill esophagitis". Other drugs including tetracyclines, clindamycin, ascorbic acid, iron supplements and bisphosphonates (e.g. alendronate) may also cause pill esophagitis and the histologic changes produced are similar. The basic disease mechanism of mucosal damage is poor swallowing and lodgement of pills at the level of the aortic arch or in the distal esophagus. Ineffective swallowing may be promoted by ingestion of pills when the patient is in a horizontal position or by taking inadequate amounts of water.
The contents of the pills are caustic and release of drugs from the core produces inflammation and eventually ulceration. Endoscopically, lesions present as discrete “punched out” ulcers with relatively little damage to adjacent mucosa. Histologically there is neutrophil infiltration, erosions or deep ulcers. Occasionally polarizable crystalline pill remnants can be identified.

There is some evidence that NSAIDs given in standard doses is harmful to the esophagus and promotes esophagitis, esophageal ulcers and stricture formation.

**Stomach and Duodenum:** A number of gastric lesions are described in patients that are taking NSAIDs. These include erosive gastritis, erosive duodenitis, deep ulcers (stomach and duodenum) and reactive gastropathy. Erosive gastritis may be hemorrhagic or non-hemorrhagic. Ulcers secondary to NSAIDs tend to be deeper and larger than the usual type of peptic ulceration. Reactive gastropathy (also known as chemical gastitis) probably occurs in between one third and one half of patients taking NSAIDs. Endoscopically, it is characterized by mucosal redness. Histologically, there is foveolar hyperplasia resulting in a corkscrew appearance. The individual cells show cytoplasmic mucin depletion with enlarged nuclei and prominent nucleoli. The lamina propria is congested and edematous. Small tongues of muscle from the muscularis mucosae may extend into the lamina propria as far as the surface epithelium. The lamina propria shows no increase in inflammatory cells. Reactive gastropathy secondary to NSAIDs is often patchy because the pills break up into small fragments. A more diffuse antral distribution of reactive gastropathy suggests the possibility of duodenal reflux and increased mucosal surface cell lost secondary to the cytotoxic properties of bile.

The underlying pathogenesis of reactive gastropathy is increased exfoliation of cells from the mucosal surface and the mucosal hyperplasia is a compensatory reaction. If the rate of exfoliation exceeds the rate of epithelial regeneration then an erosion will develop. Continued use of NSAIDs will result in frank ulceration and expose the patient to the possibility of complications such as bleeding and perforation.

**Lower gastro-intestinal tract:** NSAIDs may also produce ulcers in the distal small bowel and proximal colon. The pathogenesis of small bowel ulcers is similar to that of esophageal ulceration: local irritative effect. Bile has the effect of promoting this damage and suppression of prostaglandins does not seem to be involved. It is interesting to note that ligation of the bile duct prevents small intestinal damage by NSAIDs.

Multiple colonic lesions have been attributed to NSAIDs. The list includes: non-specific colitis, erosions, ulcers, diaphragm disease, collagenous colitis, lymphocytic colitis, pseudomembranous colitis, eosinophilic colitis and apoptotic colonopathy. They may also exacerbate ulcerative colitis and diverticular disease. Ulceration in the colon may
be due to direct mucosal irritation by the drugs or it may be secondary to suppression of
prostaglandin production. Colonic ulcers are “non-specific” histologically and resemble
the NSAIDs induced ulcers in the stomach and esophagus. Typically they are sharply
circumscribed with dense fibrosis at the base. Inflammation is usually scanty and
confined to the immediate ulcer edge. They have some features similar to ischemic
ulceration. In older literature NSAIDs ulcers were often referred to as “solitary ulcer of
the cecum” and considered to be ischemic in etiology. This was an inappropriate
designation as the ulcers are commonly multiple and not confined to the cecum.

Diaphragm disease is a rare complication of NSAID therapy. It mainly involves the small
bowel but occasionally may affect the proximal large bowel. Histologically diaphragms
consist of a thin incomplete membrane composed of a central fibrous core and covered
by normal or attenuated mucosa. At the inner edge of the membrane there is often non-
specific ulceration. Fibrosis may extend into the submucosa of the adjacent tubular
bowel but generally the muscular component of the bowel wall is unaffected.

One common effect of NSAIDs is to promote epithelial apoptosis. In turn this leads to
increased epithelial turnover with loss of cells that could contain pre-cancerous
mutations. This is one of the proposed benefits of taking low-dose aspirin on a daily
basis. It follows therefore that biopsies from patients taking this medication may
demonstrate increased apoptosis. This change has been demonstrated in gastric and
colo-rectal biopsies.

**PROTON PUMP INHIBITORS (PPIs)**

Patients treated with PPIs will inevitably develop hypoclorhydria. This leads to antral G
cell hyperplasia and hypergastrinemia which in turn leads to hyperplasia and
hypertrophy of parietal cells and hyperplasia of ECL cells in the gastric body. Initially
hyperplasia of the ECL cells (histamine producing) is linear but with continued
stimulation nodularity may develop. Unlike ECL stimulation in cases of pernicious
anemia it is unusual for neuroendocrine neoplasms (micro carcinoids) to develop.

Gastrin stimulation of parietal cells leads to cytoplasmic expansion and proliferation.
Parietal cells may extend downwards to deeper levels of the mucosa where they appear
to crowd out chief cells. They may also expand upwards into the gastric foveolae.
Morphologic changes consist of gland dilatation with swelling and bulging of individual
cells (parietal cell profusion). The cells lining the gland therefore produce a serrated
rather than a smooth outline. The cytoplasm of the parietal cells becomes paler and
may ultimately become vacuolated as the canalicular system expands.

PPIs have also been associated with the development of fundic gland polyps. Polyps
are present in 17% of individuals after three months treatment and in 35% after five
months treatment. Reports suggest that the polyps will regress after PPI treatment is
stopped but will reappear when treatment is re-started. Histologically, the polyps
themselves are an exaggerated version of PPI changes in flat mucosa with parietal cell
overgrowth and cyst formation.

It is rare to be able to identify *Helicobacter pylori* organisms in patients who are taking
PPIs long-term. However, some authors have identified overgrowth of non-specific cocci
and bacilli. This presumable represents oral contamination with growth in the absence
of stomach acid.

**INTESTINAL DISEASE SECONDARY TO CHEMOTHERAPY AND RADIOTHERAPY**

The effects of cancer chemotherapy and radiotherapy on tissues are similar. Low doses
produce degenerative changes within epithelial cells that are accompanied by non-
specific lamina propria inflammation. These changes persist for about four months
following treatment after which they gradually resolve. Intermediate doses will result in
permanent damage usually in the form of atrophy. This includes loss of glands
(particularly oxyntic glands), intestinal metaplasia and crypt shortening and distortion
(small and large intestine). Larger doses may produce deep, non-healing ulcers.

Epithelial cytologic changes that accompany epithelial regeneration have to be
distinguished from dysplasia. Chemo-radiotherapy changes are characterized by: 1)
Enlarged vesicular nuclei with prominent but irregular nucleoli, 2) Cytoplasmic
degenerative changes with vacuolation and eosinophilia. 3) Syncytial change in the
surface epithelium. 4) Atypia of fibroblasts and endothelial cells. 5) Absence of atypical
mitoses, 6) Changes affect the glands and foveolae of the stomach.

In the stomach chemotherapy changes are most frequent following hepatic arterial 5FU
infusion for the treatment of primary and secondary liver cancer. In the colon
radiotherapy changes are commonly seen alongside recto-sigmoid carcinomas that
have been treated prior to total mesenteric excision. Radiotherapy changes that are
seen closely mimic chronic ulcerative colitis with dysplasia. However, the main
distinguishing feature is uniformity of changes following radiation versus patchy
dysplasia in inflammatory bowel disease.

**ANTIBIOTICS**

Some antibiotic tablets are large (e.g. tetracycline, doxycycline) and difficult to swallow.
They may lodge in the esophagus and cause localized inflammation with erosion and
ulceration (pill esophagitis).

Antibiotics are associated with the development of pseudomembranous colitis.
However, this is not a direct toxic effect of the drug. The normal colonic flora may be
destroyed leading to an overgrowth of cytotoxin producing *Clostridium difficile*. Blood
volume depletion in patients with pseudomembranous colitis may produce ischemic changes in addition to the pseudomembranes.

Antibiotic associated hemorrhagic colitis (AAHC) may produce a clinical and pathologic picture resembling colonic ischemia. The pathogenesis is unknown. Antibiotics primarily implicated in causing this condition include penicillin derivatives such as ampicillin and amoxicillin. Rarely macrolides, cephalosporin, chloramphenicol, fluoroquinolones, and tetracycline have been implicated. This condition is more commonly recognized in Japan than in North America. This may relate to differences in normal bowel microflora.

**POTASSIUM CHLORIDE**

Potassium replacement may be prescribed for patients on diuretics. Many pharmacologic preparations are designed for “slow-release” of the drug. If this does not occur, localized damage to gastrointestinal mucosa may occur and the effects can be very similar to those of NSAIDs. Specifically, lesions that have been identified include: 1) Pill esophagitis with or without fibrous strictures. 2) Gastric, small and large bowel erosions, erosions, ulcers and fibrous strictures.

**DRUG MEDIATED ISCHEMIC COLITIS**

A wide variety of drugs have been implicated. These include: antibiotics, appetite suppressants (phentermine), chemotherapeutic agents (taxanes and vinca alkaloids), constipating agents (mechanism of action may be via fecal impaction), decongestants (pseudoephedrine), digitalis (vasoconstriction of splanchnic circulation), diuretics (lower circulating blood volume), ergot alkaloids (vasoconstriction), steroid hormones (thrombosis), amphetamines, cocaine, interleukins, tricyclic antidepressants and phenothiazines, (See reference Hass AJ et al for detailed information).

**SODIUM PHOSPHATE ENEMAS AND LAXATIVES**

Preparations used for bowel preparation prior to colonoscopy can themselves be a cause of colitis. This is particularly true where purgatives based on sodium phosphate are used. They may cause low-grade focal colitis and increase epithelial apoptosis (apoptotic colopathy). Laxatives may also increase apoptosis and there is an association between this finding and melanosis coli.

**ALENDRONATE**

This drug is used for treating osteoporosis and other bone disorders. Its use has been associated with pill esophagitis and gastro-duodenal ulceration. Crystals may sometimes be seen in the base of the ulcers.

**IRON**
Orally ingested iron may cause damage to the upper GI tract. Two patterns of injury are noted: 1) Pill esophagitis with ulceration. Blackish crystalline material may be demonstrated in the base of ulcers. 2) Gastric iron deposition within foveolae, glands and lamina propria. In both instances histochemical stains for iron (Perl's Prussian blue reaction) will be positive.

**KAYEXALATE**

Kayexelate is an ion exchange resin which is active in the small bowel where it exchanges sodium ions for potassium ions in the treatment of hyperkalemia. It may cause erosions and ulcers within the esophagus, stomach and duodenum. In the base of the ulcers non-polarizable rhomboid or triangular crystals are present. These crystals stain red with PAS/D and acid fast stains.

**COLCHICINE AND TAXOL**

Taxol is an anti-cancer agent. Colchicine is used in the treatment of gout. Both drugs interfere with tubulin and inhibit its polymerization. This causes mitotic arrest. Histologically ring-shaped mitotic figures may be seen in the proliferation zones of the esophagus, stomach and duodenum.

**MYCOPHENOLATE**

Mycophenolate is used in organ transplant patients for prevention and suppression of acute rejection. Colonic biopsies from patients taking these drugs show changes in up to 70% of cases. A variety of changes have been described and these may occur as isolated findings or in combination. These include apoptosis, architectural distortion and crypt atrophy, IBD-like changes, GVHD-like changes, ischemia-like changes and self-limited colitis-like changes.

**PANCREATIC ENZYME REPLACEMENTS**

This topic is of historic interest only as the drugs responsible for fibrosing colonopathy have now been withdrawn from use. Formerly, high-strength pancreatic enzymes were combined with methacrylic acid and caused segmental fibrous strictures particularly in the proximal colon. Biopsies of the strictures showed increased intramucosal eosinophils.

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DRUG INDUCED INJURY OF THE G.I. TRACT

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NSAIDs INDUCED GI INJURY

- Pill esophagitis, ulcers and strictures
- Erosive gastritis and duodenitis
- Gastric and duodenal ulcers
- Reactive gastropathy
- Distal ileal ulcers
- Proximal colonic ulcers and focal colitis
- Diaphragm disease
- Collagenous and lymphocytic colitis
- Increased apoptosis
PROTON PUMP INHIBITORS (PPIs)

- Hypertrophy and hyperplasia of parietal cells
- Hyperplasia of ECL cells
- Gland dilatation
- Parietal cell “snouting”
- Parietal cell cytoplasmic vacuolation
- Fundic gland polyps
CHEMOTHERAPY AND RADIOTHERAPY

• **Early changes**: Non-specific inflammation and cytologic changes consisting of 1) Syncytial change in surface epithelium 2) Enlarged vesicular nuclei and irregular nucleoli 3) Cytoplasmic eosinophilia and vacuolation

• **Chronic changes**: Mucosal atrophy and intestinal metaplasia, non-healing ulcers, stricture formation
ANTIBIOTICS

• Pill esophagitis (tetracycline, doxycycline)
• Pseudomembranous colitis
• Antibiotic associated hemorrhagic colitis (AAHC) (ampicillin, amoxicillin, macrolides, cephalosporin, chloramphenicol, fluoroquinolones, tetracycline).
• Histologically and clinically AAHC resembles acute colonic ischemia
POTASSIUM CHLORIDE

- Pill esophagitis with or without fibrous strictures
- Gastric, small bowel, large bowel erosions, ulcers and fibrous strictures
DRUG MEDIATED ISCHEMIC COLITIS

- Antibiotics
- Phentermine
- Chemotherapeutic agents (Taxol, vinca alkaloids)
- Constipating agents (fecal impaction)
- Decongestants (pseudoephedrine)
- Digitalis, ergotamine, cocaine (vasoconstriction)
- Diuretics (lower blood volume)
- Steroid hormones (thrombosis)
ENEMAS AND LAXATIVES

• Melanosis coli
• Apoptotic colopathy
ALENDRONATE

• Alendronate is used for treating patients with osteoporosis or other bone disease
• May cause esophageal, gastric and duodenal ulceration. Crystals (non-specific) may be present in the base of the ulcers
IRON

• Localized inflammation with ulceration especially in esophagus, stomach and duodenum (crystalline material present in the base of the ulcers)

• Gastric and small bowel deposition within epithelium, glands and lamina propria

• Ingested iron, hemosiderin and iron in hemochromatosis will all be Prussian blue positive
COLCHICINE AND TAXOL

- Ischemic colitis
- Ring shaped mitotic figures may be seen in proliferation zones in all areas of the gastrointestinal tract
MYCOPHENOLATE

- Mycophenolate is used to prevent and suppress acute rejection
- Produces a colitis characterized by apoptosis, architectural distortion, crypt atrophy, IBD-like changes, GVHD-like changes and ischemia-like changes
KAYEXELATE

• Kayexalate is an ion exchange resin that is active in the small bowel where it exchanges sodium ions for potassium ions in the treatment of hyperkalemia

• Kayexalate crystals are triangular or rhomboid in configuration and are basophilic on routine sections. They are PAS/D positive

• Apart from the presence of crystals the ulcers are non-specific in type
PANCREATIC ENZYME REPLACEMENTS

• Of historical interest only: Thought to be related to high dose enzyme therapy and methacrylic acid in the formulation (this medication is now withdrawn)

• Changes consist of localized fibrous strictures in the proximal colon with increased numbers of eosinophils in overlying mucosa (fibrosing colonopathy)
NO PASSING A GRASS