INTERSTITIAL CYSTITIS AND GASTROINTESTINAL DISORDERS

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Many patients with interstitial cystitis (IC) also have gastrointestinal disorders. Table 1 shows the results of a survey in the United States in which more than 6,000 IC patients were asked what disorders they had in association with their IC. Our own data on IC and Sjögren's syndrome have been added to this list. Two groups of gastrointestinal disorders are included in this list: irritable bowel syndrome and Crohn's disease/ulcerative colitis. Both groups will be discussed here individually.

Table 1. *Prevalence of associated disorders in patients with interstitial cystitis (IC)*

	Prevalence (%)	
Diagnosis	**IC**	**General population**
Allergy	41-47	22.5
Irritable bowel syndrome	25.4	2.9
Sensitive skin	22.6	10.6
Vulvodynia	10.9	15.0
Fibromyalgia	12.8	3.2
Chronic fatigue syndrome	7.7	8.5
Migraine	18.8	18.0
Asthma	9.2	6.1
Crohn's disease/ulcerative colitis	7.3	0.07
Thyroid disease	7	?
Rheumatoid arthritis	4-13	1-2
Systemic lupus erythematosus	1.7	0.05
Sjögren's syndrome	8.0	0.5

In addition to the above-mentioned disorders, drugs can also be the cause of gastric or intestinal symptoms. In particular, certain painkilling/anti-inflammatory drugs often cause gastrointestinal symptoms or disorders. These will be discussed separately.

Crohn's disease

Crohn's disease is a chronic inflammatory bowel disease. This disease is known by a variety of names depending on which parts of the intestinal tract are affected. If the disease only occurs in the last section of the small intestine, the ileum, it is also known as terminal ileitis or regional ileitis. If the disease is present in the large intestine, it is called Crohn's colitis (see Figure 1).

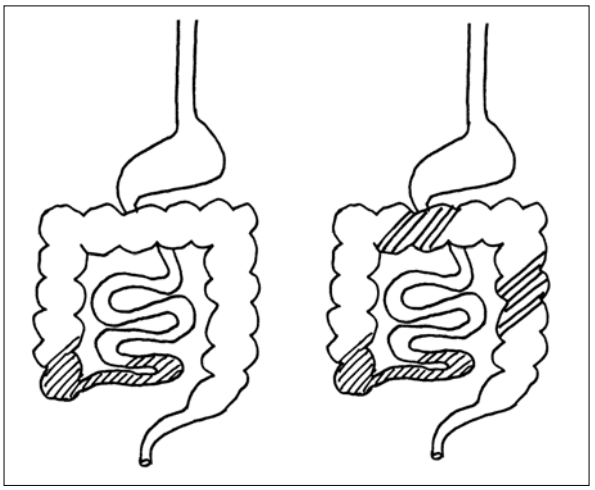

Figure 1. *In the left figure, the striped area indicates the site of Crohn's disease in the small intestine and the first section of the large intestine (caecum). In the right figure when the disease is present in the large intestine with skip lesions (see text for further details)*

Disease manifestations

Diseased segments of intestine often alternate with normal segments of intestine. The diseased segments are then known as skip lesions. The disease can also occur in both the large and small intestines. In principle it can occur in any part of the intestinal tract, but the most common sites are the small intestine and large intestine. In addition, many patients have other abnormalities, for instance around the anus. These may be fistulas, fissures or abscesses. Fistulas are small tunnels in the tissue that connect the cavities between two organs (for example: two separate parts of the intestines, between the intestines and the bladder or between the intestines and the vagina) or the cavity of one organ with the surface of the body. Fissures are cracks or splits in the mucous membrane, while abscesses are hollow spaces filled with pus that did not previously exist. The rectum is frequently disease-free. Fibrous tissue may form (fibrosis) in inflamed sections, leading to narrowing (stenosis) of the intestine.

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Type of inflammation

Sections of intestine that are affected are often swollen by the inflammation. Examination of intestinal tissue under the microscope often shows that the inflamed tissue contains many lymphocytes and granulomas. Granulomas are accumulations of specific cells that do not normally occur in the tissue, surrounded by lymphocytes. The inflammation is often present in all layers of the intestine. The mucous membrane, the innermost layer of the intestine, is often swollen (oedema), greatly engorged with an excess of blood (hyperaemia) and may be ulcerated.

Symptoms

The symptoms of the disease partly depend on the site(s) of the inflammation. The disease frequently begins gradually and the time that elapses between the first symptoms and the time when it is diagnosed is often four years.

If the disease is only present in the small intestine, the symptoms often consist of abdominal cramp (particularly after meals), weight loss and diarrhoea. If the disease is in the large intestine, the stools may often contain blood, which can also of course result in loose stools. In addition, patients with Crohn's disease are often anaemic for a number of reasons such as chronic blood loss, the inflammation itself, folic acid deficiency (in the case of inflammation of the jejunum) or a vitamin B_{12} deficiency (if the last section of the small intestine, the ileum, is affected).

Crohn's disease is not always restricted to the intestines. Extra-intestinal symptoms (outside the intestines) may also occur in this disease (see Table 2).

Extra-intestinal symptoms of Crohn's disease

Pyoderma gangraenosum

Pyoderma gangraenosum is a non-bacterial, ulcerative inflammatory condition of the skin. This disorder can be very persistent and mainly occurs in serious forms of Crohn's disease or ulcerative colitis (see below).

Table 2. *Possible complications of Crohn's disease that can occur outside the intestines (see text for further details)*

extra-intestinal symptoms (= outside the intestines)
· pyoderma gangrenosum
· erythema nodosum
· aphthae
· inflamed eyes: cornea (conjunctivitis) , iris, sclera (scleritis)
· sclerosing cholangitis (narrowing of the bile ducts)
· inflammation of joints (especially large joints, asymmetric)
· sacroiliitis (pelvis) and spondylitis (vertebrae)
· spondylitis ankylopoietica (=Bechterew's disease)

Erythema nodosum

Erythema nodosum is inflammation of subcutaneous tissue, usually on the front of the lower legs. Erythema nodosum also occurs in numerous other diseases such as tuberculosis, sarcoidosis, streptococcal infections and as a hypersensitivity reaction to certain drugs, especially those containing sulpha.

Aphthae

Aphthae are ulcers in the mouth that may likewise be found in many other disorders.

Inflammation of the eyes

Inflammation of the eyes may occur, such as that of the cornea (conjunctivitis), iris (iridocyclitis, uveitis) and sclera (scleritis).

Arthritis

Arthritis (inflammation of joints) is mainly seen in Crohn's disease in the large intestine and also in ulcerative colitis. It frequently concerns the large joints such as ankle or knee, often asymmetrically.

Spondylitis ankylopoietica

Spondylitis ankylopoietica (= Bechterew's disease) is an inflammatory condition of the joints of the pelvis and spinal column. The hip and shoulder joints may also be affected, but other joints are less common. People with Crohn's disease or colitis ulcerosa are more susceptible to this disease than others. Many patients with spondylitis ankylopoietica have a specific blood group of the so-called HLA system ("transplantation antigens"), the HLA-B27 type. This blood group normally occurs in 10% of the population as opposed to 90% of the people with spondylitis ankylopoietica.

Cause

Although the cause of Crohn's disease is unknown, it is often assumed to be an autoimmune disease. It occurs in approximately 1 in 10,000 people and is just as common in men as in women. Although there may frequently be more than 1 person in a family affected by the disease, there is no evidence that the disease is contagious.

Treatment

Crohn's disease is treated with anti-inflammatory drugs, ranging from prednisone, sulphasalazine and azathioprine to more modern, often still experimental drugs that suppress the immune system. If sections of intestine have become narrow as a result of the formation of fibrous tissue, the only possible treatment

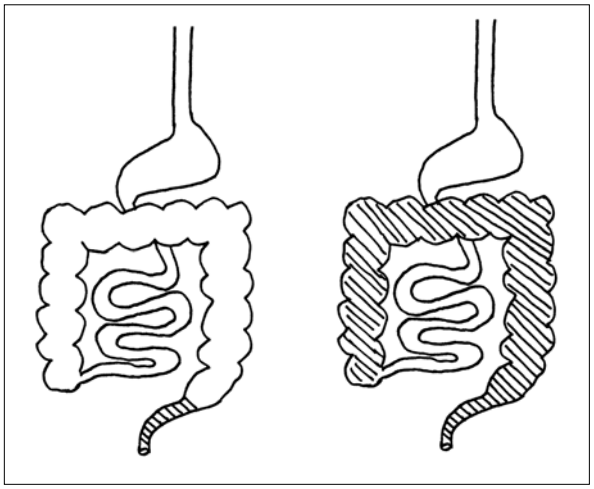

Figure 2. *In the left figure, the striped areas indicate ulcerative colitis in the rectum and in the right figure they show the presence of the disease throughout the large intestine (see text for further details)*

may be for the diseased sections of the intestine to be removed surgically. Because Crohn's disease often recurs in other sections of the intestine, the greatest restraint is exercised with regard to surgery.

Ulcerative colitis

Ulcerative colitis is an intestinal disease that resembles Crohn's disease but has a number of significant differences. Ulcerative colitis only occurs in the large intestine (colon), sometimes only in the rectum, but never in other parts of the intestine (see Figure 2). The disease often begins quite suddenly, formation of fibrous tissue with stenosis rarely occurs and fistulas virtually never.

Symptoms

The main symptoms of ulcerative colitis are loss of blood from the rectum, diarrhoea, fever, abdominal pain and weight loss. Periods with disease symptoms alternate with symptom-free periods. The disease is limited to the mucous membrane and does not penetrate the entire wall of the intestine. Fistulas are rare and granulomas virtually never occur in the tissue.

As in the case of Crohn's disease, extra-intestinal symptoms may also occur. The cause of ulcerative colitis is unknown. In general terms, treatment is similar to that of Crohn's disease.

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is not an inflammatory condition of the intestines like the diseases discussed above, but is a disorder of the function of the intestines, possibly the motor function (movement) of the intestines. The symptoms are an abnormal pattern of bowel movements and abdominal pain. There are two types of IBS. In 20% of the people with irritable bowel syndrome, the problem solely consists of painless diarrhoea. In the remaining 80%, the symptoms consist of abdominal pain, diarrhoea or constipation, or constipation alternating with diarrhoea. This form is also sometimes called *spastic bowel* or *spastic colitis*. IBS generally starts in adulthood and is seen 4x more frequently in women than in men.

Disease manifestations

The diarrhoea only occurs during the daytime and is usually a question of small amounts. The diarrhoea may be exacerbated by eating and emotional stress. There is often mucus with the stools but not blood (unless the constipation has also caused haemorrhoids).

Table 3. *Adaptation of diet and lifestyle as treatment for irritable bowel syndrome*

1.	**high-fibre "bulk"-forming foods** examples: bran, psyllium *gradually* increase the quantity and drink plenty of liquids fibre binds moisture: liquid stools become more solid while hard stools become softer in 20%: first of all an increase in symptoms, after a few weeks an improvement
2.	**do not ignore the urge to have a bowel movement** get into the habit of going to the toilet at a fixed time every day (after breakfast)
3.	**diet**: symptoms may be exacerbated by coffee, sorbitol (artificial sweetener), milk products, certain vegetables, cabbage
4.	**change your lifestyle** eat, exercise and relax on a regular basis
5.	**diarrhoea** if necessary, loperamide 2 mg (Imodium®) for preventive and occasional use
6.	**gas** · eat slowly · do not chew chewing-gum · do not drink carbonated drinks or drinks containing caffeine · do not use artificial sweeteners (sorbitol) · do not eat cabbage
7.	**avoid non-steroidal anti-inflammatory drugs** NSAIDs for short, also called prostaglandin synthesis inhibitors this group of drugs causes or increases constipation

Table 4. *A comparison of a number of characteristics of Crohn's disease, ulcerative colitis and irritable bowel syndrome*

disease	Crohn's disease	ulcerative colitis	irritable bowel syndrome
characteristics	inflammation of large and/or small intestines; skip lesions	inflammation of mucous membrane of rectum and/or large intestine	functional disorder of the movement of the intestines
features	abdominal pain loose stools weight loss anaemia (vit. B_{12})	abdominal pain diarrhoea blood and mucus in stools anaemia (iron deficiency)	abdominal pain constipation and diarrhoea mucus in stools bloated abdomen no weight loss no diarrhoea at night
medical treatment	anti-inflammatory drugs	anti-inflammatory drugs	none
diet	normal diet	normal diet	high-fibre, bulk-forming foods avoidance of certain foods if possible

The location and severity of the abdominal pain can vary, with occasional periods of painful cramp. The abdominal pain is exacerbated by eating and stress, but improved by breaking wind and by going to the toilet. The diarrhoea and abdominal pain of IBS are often at their worst in the morning. The patient goes to the toilet a number of times in succession and then no more for the rest of the day. There appears to be an increase in gas formation in the intestines in the form of wind and a bloated, rumbling abdomen. It is possible that there may in fact be no real increase, but simply that the upper sections of the intestines contain more gas and the lower ones less. 25-50% of the people with IBS also have stomach disorders in the form of a heavy, uncomfortable, burning sensation (dyspepsia), nausea and sometimes even vomiting.

Cause

The cause of IBS is probably an abnormality in the control of the movement of the intestines by the nervous system. There are normally 6 peaks of electric activity in the intestines every minute, in the case of IBS there are only 3 a minute. Investigation of the intestines reveals no visible abnormalities. The diagnosis can only be made on the basis of the typical symptoms and if no abnormalities are found in intestinal investigations.

Treatment

Treatment consists of adapting diet and lifestyle (Table 3).

A comparison of Crohn's disease, ulcerative colitis and irritable bowel disease

The main differences have been summarised in table 4. On the basis of signs and symptoms, it is not usually difficult for a physician to tell whether a patient has Crohn's disease, ulcerative colitis or irritable bowel syndrome, although the latter diagnosis also requires intestinal investigations just to be sure.

Weight loss, blood in the stools and diarrhoea at night indicate an inflammatory bowel disorder such as Crohn's disease or ulcerative colitis.

Alternating hard and soft stools with mucus, especially in the morning and never at night, without weight loss or blood in the stools, are more likely to indicate irritable bowel syndrome. In the case of patients with IBS, it is not only important to give advice on how to reduce the symptoms but also to discover the background to the symptoms so as to prevent unnecessary worry.

It is unclear why patients with IC have these gastrointestinal diseases or disorders more frequently than the general population, although - quite apart from the site of the problem (intestines against the bladder) - there are indeed similarities. These concern abnormalities in the movement of the smooth muscle tissue, the type of inflammation process and the occurrence of ulcers.

Painkilling/anti-inflammatory medication

There are many types of medication with painkilling and/or anti-inflammatory properties. The most commonly known example is "aspirin", a so-called prostaglandin synthesis inhibitor.

It is particularly the prostaglandin synthesis inhibitors (PSIs) that can have undesirable effects on the intestines. This group may be subdivided into two groups: older PSIs that inhibit both the enzyme cyclo-

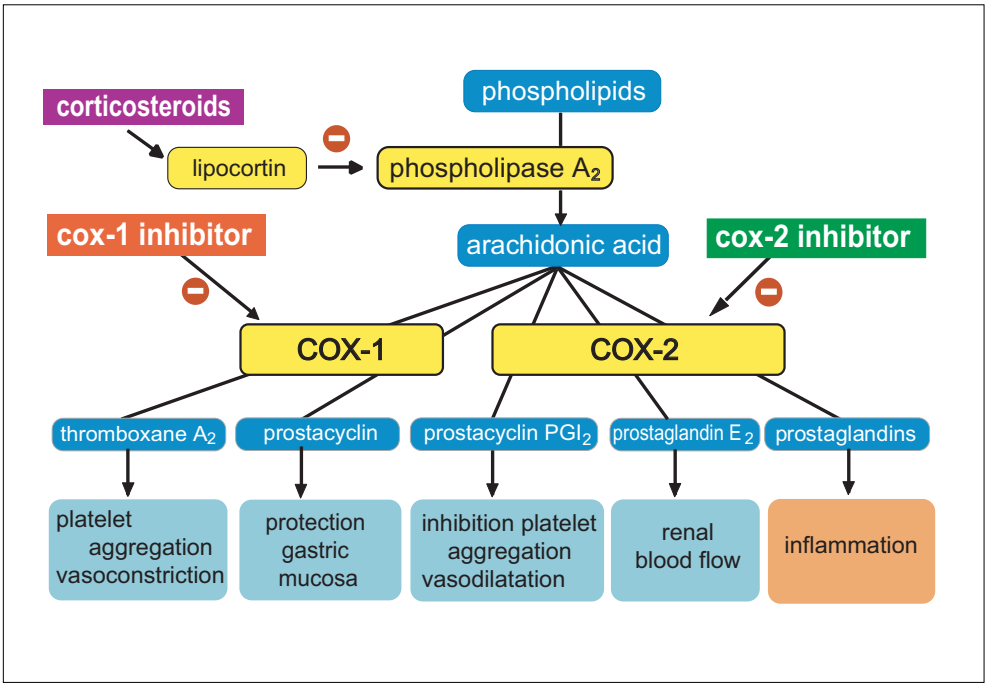

Figure 3. *Simplified schematic representation of the development of inflammatory symptoms and the processes affected by the prostaglandin synthesis inhibitors.*

oxygenase I (cox-1) and cyclo-oxygenase II (cox-2) and the more modern PSIs that only inhibit cox-2. This last group is often referred to as *coxibs*.

Table 5 shows the substance (generic, not brand-names) names of a number of PSIs, classified according to which enzyme they inhibit.[1,2]

Figure 3 shows how inflammatory symptoms develop and which processes are inhibited by the PSIs. When tissue damage occurs, arachidonic acid is formed from phospholipids of the membrane of leukocytes (white blood cells). Under the influence of the cox-1 and cox-2 enzymes, arachidonic acid is converted into other substances whose function greatly differs. Cox-1 is responsible for the formation of substances that play an important role in the clotting (aggregation) of platelets, replenishment of the gastric mucous membrane and normal blood flow regulation in the kidneys. Cox-2 also plays a role in the kidney function, but mainly in connection with the formation of prostaglandins that cause inflammatory symptoms. Therefore, only inhibition of cox-2 is necessary to inhibit inflammatory activity. Since the older PSIs inhibit both cox-1 and cox-2, this means that in addition to the desired inhibition of the inflammation, undesirable effects also occur such as inhibition of the aggregation of platelets (result: impaired blood clotting), inhibited replenishment of the gastric mucous membrane (result: erosions and ulcers) and inhibited blood flow regulation in the kidneys (result: impairment of the kidney function in the case of a pre-existing kidney disorder). The combination of damage to the gastrointestinal mucous membrane and impaired blood clotting can cause gastrointestinal bleeding. In the United States this causes 16,500 fatal gastrointestinal haemorrhages annually [3] and in the Netherlands an estimated 600-800 such cases.

The new, selective cox-2 inhibitors do not diminish the aggregation of platelets [4] and cause less frequent damage to the gastrointestinal mucous membrane. [5-11] This greatly reduces the risk of haemorrhages. A disadvantage is that they are more expensive than the older PSIs. However, if the total cost is taken into account (such as extra medication to protect the

Table 5. *Examples of anti-inflammatory and painkilling drugs of the prostaglandin synthesis inhibitor type, classified according to which of the two enzymes cyclo-oxygase I or II (COX-1 and COX-2) they mainly inhibit.*

Inhibition of		
cox-1 and cox-2	**cox-2 greater than cox-1**	**selective cox-2**
acetylsalicylic acid	diclofenac	rofecoxib [b]
indomethacin	meloxicam	celecoxib
ibuprofen	nabumetone	etoricoxib
naproxen		valdecoxib [b]
piroxicam		
tenoxicam		
tiaprofenic acid [a]		

[a] tiaprofenic acid can sometimes cause IC-type bladder disorders and symptoms.
[b] withdrawn from the market

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stomach and the cost of investigations and hospital admission in the case of haemorrhages), the cost is similar. [12] In the coming years, we are likely to see more selective cox-2 inhibitors appearing on the market, while the older types will gradually disappear. It is particularly ironic that the safer PSIs are only available on prescription, while many of the old, more dangerous PSIs can be purchased over the counter.

The selective cox-2 inhibitors can be combined if necessary with "children's aspirin", unlike ibuprofen and indomethacin, for example, that render "children's aspirin" ineffective.[13] By "children's aspirin" we mean a low dose of some form of the old-style "aspirin" used for its effect on the platelets and not as an anti-inflammatory or painkiller. Its purpose is to improve the blood flow in the brain or heart, for example. Due to the low dosage (e.g. 38 mg/day) of this children's aspirin, the risk of gastrointestinal bleeding is virtually nil.

Side effects of coxibs

The selective cox-2 inhibitors unfortunately have the same adverse effects as the older PSIs in the form of a possible increase in blood pressure, impairment of the kidney function in the case of a pre-existing kidney disorder, fluid retention and constipation. This last aspect is of special importance to IC patients with irritable bowel syndrome.

In the treatment of cardiovascular disease, inhibition of the function of platelets (a cox-1 effect) is often desirable. This can be achieved in a safe manner by low doses of aspirin. Coxibs naturally do not have this effect and do not offer protection from cardiovascular disease. On the contrary, it has recently been shown that the risk of thromboembolic events may be increased due to inhibition of the platelet aggregation inhibiting effect of the prostaglandin PGI_2. The strength of this effect possibly depends on the dosage and duration of treatment. However, recent information suggests that the old NSAIDs (except naproxen) similarly increase the risk of thromboembolic events. Cardiovascular or thrombotic disease and risk factors (use of oral contraceptives ?) are therefore contra-indications for many NSAIDs and coxibs. If necessary in these situations, coxibs but not old NSAIDs can be combined with low-dose aspirin to protect against thrombotic cardiovascular events.

Well-known side effects of the old NSAIDs such as urticarial reactions or AERD (Aspirin Exacerbated Respiratory Disease) do not usually occur with coxibs.

Conclusion

The conclusion is that if the use of anti-inflammatory painkilling drugs is necessary, the best choice of NSAID is a coxib. The highest doses should be avoided as far as possible. Cardiovascular or thrombotic disease and risk factors are contraindications for many old NSAIDs as well as the coxibs. The coxibs that are available today (celecoxib and etoricoxib) can be combined with low dose aspirin.

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