



Drugs

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This booklet describes the drugs used in IBD how they work, when they are used and their more common and important side-effects. The list of side-effects is not all inclusive. If you think one of your drugs is causing a side-effect, consult your doctor. It is important not to treat yourself. The booklet does not discuss any non-drug therapies such as dietary changes, surgery or psychological support. You can obtain further information about these forms of treatment through the Crohn's and Colitis Support Group.

Many drugs are used to treat inflammatory bowel disease (IBD). They may be given for a variety of reasons: 1) to suppress inflammation in those with active disease, 2) to prevent flare-ups in those with inactive disease, 3) to control symptoms such as pain or diarrhoea, or 4) to replace or supplement essential nutrients which are poorly absorbed because of extensive disease or surgery. They are given in a number of ways depending on the location and severity of disease; as tablets or capsules, by intravenous or intramuscular injection, or as enemas, rectal foam or suppositories.

As the cause of IBD is not known, the drugs cannot be precisely targeted and even the "specific" drugs used to suppress inflammation or prevent flare-ups have a wide range of effects, some beneficial and some not. All treatments used in medicine (drugs, surgery, radiation) have risks. Every time a doctor prescribes a drug, the risks of the drug must be weighed against the risks of continuing or worsening symptoms and also the development of complications if the drug is not used.

People taking these medications should also be aware of possible "generic" side-effects of particular medications. For example, some tablets contain lactose to

which some people are allergic and tablets may be very big and hard to swallow.

The potential benefits and risks of any therapy should be fully considered by you and your doctor.

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A. SPECIFIC DRUGS

1. *Drugs containing 5-aminosalicylic acid (5-ASA)*

Nearly all individuals with ulcerative colitis and many with Crohn's disease take 5-aminosalicylic acid, or 5-ASA, which is chemically related to aspirin. 5-ASA is useful for the treatment of mild attacks of ulcerative colitis or Crohn's disease but its main role is in patients with inactive ulcerative colitis, where it markedly reduces the chance of a flare-up. Taking 5-ASA does not guarantee that you will remain well but it does significantly lower the risk of a flare-up. This effect probably persists indefinitely and most patients with ulcerative colitis take a 5-ASA containing drug for life. There is no evidence that this long-term use is harmful. Research suggests that 5-ASA may also have some effect in preventing flare-ups of Crohn's disease.

To be effective 5-ASA must remain in the bowel until it reaches the area which is diseased. If pure 5-ASA is taken by mouth, it is completely absorbed from the upper gut into the blood. As all ulcerative colitis and some Crohn's disease occurs in the large bowel (or colon), which is beyond the site of absorption, it is necessary to modify 5-ASA to prevent it being absorbed in the upper gut. There are three 5-ASA preparations available in NZ. Most studies have found them to be equally effective, both in the treatment of mild attacks of ulcerative colitis and in preventing flare-ups.

1.1 *Sulphasalazine (Salazopyrin®)*

Sulphasalazine is 5-ASA chemically linked to sulphapyridine, a sulphur antibiotic. Sulphasalazine is not absorbed into the blood from the upper gut and cannot be broken down by the body. However, bacteria in the large bowel break the link between sulphapyridine and 5-ASA, releasing free 5-ASA into the bowel. There is very little absorption of 5-ASA from the large bowel. In contrast sulphapyridine is almost completely absorbed into the blood and is thought to be responsible for most, but not all, of the side-effects of sulphasalazine. You should not take sulphasalazine if you are allergic to sulphur antibiotics. You should also tell your doctor if you think you are allergic to aspirin

or if you have had a reaction to other types of drugs which may contain sulphur, such as diuretics (water pills) or tablets for diabetes.

1.1.1 *Side Effects of Sulphasalazine*

About 10% of individuals are unable to tolerate sulphasalazine because of side-effects. These usually occur within a few weeks of starting the drug and are more frequent with high doses (more than 4 tablets per day). In general it is best to start with a lower dose and gradually build it up.

The most common side-effects are abdominal pain, nausea and vomiting, and reduced appetite. These can be helped by taking the tablets with food, rather than on an empty stomach, or by using enteric coated tablets (Salazopyrin EN). The enteric coating prevents release of sulphasalazine from the tablet until after it has left the stomach.

Headache and skin rashes are also relatively common. Occasionally sulphasalazine causes anaemia. Rarely it can suppress the production of different types of blood cells in the bone marrow. Other uncommon side-effects include inflammation of the lung, hair loss, blistering of the face and mouth, and a flare-up of colitis.

Sulphasalazine can occasionally cause male infertility by reducing the sperm count. This is due to sulphapyridine and always resolves when the drug is stopped. Rarely it reduces the body's ability to absorb folic acid, a vitamin necessary for blood formation. This is only significant if there is increased demand for folic acid (eg. during pregnancy) or another reason for impaired folic acid absorption (eg. surgical removal of part of the small bowel) and is easily controlled by taking a folic acid tablet. Some patients taking sulphasalazine notice that their urine has an orange colour. This is harmless.

1.2 *Olsalazine (Dipentum®)*

Olsalazine is made up of two molecules of 5-ASA linked in the same way as the 5-ASA and sulphapyridine that make up sulphasalazine. Like sulphasalazine, olsalazine is not absorbed in the upper gut

but is broken down by bacteria in the large bowel, releasing 5-ASA.

As there is no sulphur component most individuals who are unable to take sulphasalazine because of side-effects can take olsalazine. However, about 10% develop watery diarrhoea soon after commencing olsalazine. This can often be improved by starting with a lower dose or by taking the drug with food, and tends to resolve with time. However, some patients are unable to take olsalazine because of diarrhoea. Other side-effects are quite rare; nausea, headache, joint pains, abdominal pain and skin rash have been reported. You should tell your doctor if you think you are allergic to aspirin.

1.3 *Mesalazine (Pentasa® , Asaco®)*

Mesalazine is 5-ASA in a slow release tablet which does not break down until it reaches the lower part of the small bowel (the ileum) and the large bowel. Some 5-ASA is absorbed into the blood after it is released in the lower small bowel. There are several varieties of mesalazine, each with different patterns of 5-ASA release.

As 5-ASA is released in the ileum the use of mesalazine for Crohn's disease affecting the ileum has been investigated over the past few years. Recent research suggests that it has some effect, both for the treatment of mild attacks and for preventing flare-ups in those whose disease is inactive. However, it is much less effective than steroids in active disease and the preventative effect is less than that of 5-ASA containing drugs in ulcerative colitis.

Most individuals unable to take sulphasalazine because of side-effects are able to take mesalazine. Side-effects are relatively uncommon but nausea, abdominal pain, headaches and rashes do occasionally occur. There have been a few reports of kidney damage, presumably due to the small amount of 5-ASA absorbed from the small bowel. You should tell your doctor if you think you are allergic to aspirin.

1.4 *ASA Enemas*

Ulcerative colitis confined to the lower part of the large bowel can be treated by drugs inserted into the rectum, most commonly by enema. This method of treatment has the advantage that large amounts of drug can be

delivered to the site of disease with very little absorption into the blood. Rectal steroids have been used for ulcerative colitis for many years.

5-ASA can also be given by enema to control attacks of ulcerative colitis affecting the lower part of the large bowel. Direct comparisons with steroid enemas suggest that 5-ASA is at least as effective and possibly even more effective. 5-ASA enemas are often useful for attacks of colitis not responding to other drugs.

5-ASA and sulphasalazine suppositories are only useful for disease confined to the lowest part of the bowel (the rectum).

2. **Corticosteroids (Steroids)**

Corticosteroids are the most effective drugs used in the treatment of moderate to severe IBD. Prednisone and prednisolone are the two steroids most commonly used for the treatment of IBD in NZ. They are derived from corticosteroid (or glucocorticoid) hormones produced by the adrenal gland which are essential for a range of bodily functions. They should not be confused with steroid sex hormones or with anabolic steroids used by body builders and athletes. More recently the steroid budesonide (Entocort®) has become available in New Zealand which delivers similar efficacy to prednisone but with fewer side-effects. Because of its site of delivery it is only appropriate for patients with ileal Crohn's disease.

Corticosteroids have a wide range of actions but their major effect in IBD is to suppress inflammation. They can be given as tablets, enemas, rectal foams, suppositories or intravenous injections, depending on the site and severity of inflammation. Rectal steroids (eg. Predsol®, Colifoam®) are preferred for disease confined to the lower large bowel because they are poorly absorbed into the blood and therefore produce fewer side-effects. There is no point in using rectal steroids for more extensive disease, as only part of the inflamed bowel will be treated. Budesonide (Entocort®) is delivered to the site of disease by packaging the drug in pellets designed to release it in the last part of the small bowel and first part of the colon. It works mainly by topical action whereas prednisone is absorbed in the blood

to a greater extent and therefore has a systemic “whole-body” action. The poor absorption of budesonide when taken as Entocort® means that 50% fewer patients will develop steroid side effects.

Although steroids are the most effective treatment for more severe IBD, their use is restricted by important side-effects. Therefore high doses are used to bring attacks under control, after which they are gradually withdrawn over weeks to months. Steroids have no role in preventing flare-ups in those with inactive disease. However, a few patients with persistent “grumbling” disease require prolonged treatment with steroids. In these cases the lowest possible dose is used.

2.1 Side-Effects of Corticosteroids

Patients with IBD are often reluctant to take steroids because of their effects on bodily appearance. However, these side-effects do not always occur. The most common changes are weight gain (predominantly face and body - sometimes a “buffalo hump” of fat develops in the middle of the upper back), rounding (or “mooning”) of the face, redness of the skin, acne, facial hair, easy bruising and ankle swelling. Rapid changes in weight can cause stretch marks. Some people develop wasting and weakness of the muscles of the upper arms and legs with long-term use. This can lead to difficulty with activities such as climbing stairs, getting out of a chair, combing hair or hanging out washing.

Many patients notice an increased appetite. Mood changes can also occur, usually a feeling of well-being but occasionally agitation, irritability or depression.

There are a number of less visible side-effects. Steroids weaken the body’s resistance to infection. You should always consult your doctor if you develop an infection while you are taking steroids. They also cause thinning of the skin and impair healing after cuts or surgery.

Steroids may raise blood sugar levels, some people who have normal blood sugar levels develop diabetes while they are on steroids, those with pre-existing diabetes may have to increase their treatment. They can also raise blood

pressure and lower the level of potassium in the blood, occasionally causing fatigue and weakness.

Prolonged use of steroids in children may retard growth. However, children with active IBD will not grow normally until the disease is brought under control. The long-term effects of withholding treatment are significantly greater than the side effects of steroids. Children with IBD often experience a growth spurt after their disease is controlled.

All of the side-effects mentioned so far are reversible, they resolve when the steroids are stopped. There are also a small number of irreversible side-effects. These include development of cataracts and most importantly, bone damage. Corticosteroids can lead to osteoporosis, or softening of bones, with the result that bones break more easily. Osteoporosis develops gradually, particularly when high doses have been used for long periods of time and is more likely in those with other risk factors (eg. women after menopause). Rarely they cause a sudden loss of blood supply to the bone of the hip joint (avascular necrosis of the head of the femur).

The body’s normal steroid production stops when you take corticosteroids. When an attack of IBD is under control the dose of steroids should be reduced gradually to allow the body to take over again. It may take up to 12 months to restore completely normal steroid production. As increased levels of corticosteroids are necessary for your body to cope with physical stresses such as surgery or illness, you should always tell your doctor, dentist or any paramedical person treating you if you have taken steroids over the previous 12 months. You should never stop taking steroids suddenly unless advised to do so by your doctor.

3. Immunosuppressive Drugs

These drugs work by suppressing the activity of the body’s immune system. They were initially developed for use in transplantation and cancer treatment. The rationale behind their use is to suppress the immune system so that it is unable to mount

an inflammatory response in the gut, but not so much that it is unable to defend the body against infections.

3.1 *Azathioprine (Imuran®) and 6-mercaptopurine (6-MP, Puri-Netho®)*

Azathioprine and 6-MP are the most commonly used immunosuppressive agents in IBD. Azathioprine, which is converted to 6-MP by the body, is more commonly used. These drugs are generally used for patients whose disease is not responding to steroids, or is only controlled by an unacceptably high dose of steroids, and for patients with frequent flare-ups. Both drugs are available in tablet form and have been in use for 20 years.

Azathioprine has been shown to control difficult Crohn's disease and ulcerative colitis, and to prevent flare-ups of both diseases. It has a "steroid sparing" effect, allowing the dose of steroids to be reduced to a level that is less likely to cause side-effects. Azathioprine may take up to 6 months to have an effect.

3.1.1 *Side-Effects of Azathioprine and 6-MP*

The most important side-effect of azathioprine and 6-MP is suppression of the bone marrow, leading to reduced production of blood cells, particularly white blood cells, which are the body's main defence against infection. Bone marrow suppression can also cause easy bruising. All patients taking azathioprine require regular blood tests and should report any signs of infection (eg. fever, chill or sore throat), bleeding or bruising immediately. Bone marrow suppression is uncommon and is reversible if the drug is stopped.

Other side effects of azathioprine include nausea, loss of appetite, fever, rashes, inflammation of the liver and abdominal pain due to inflammation of the pancreas (pancreatitis). Approximately 10% of individuals are unable to continue taking azathioprine because of side-effects. However, they all resolve when the drug is stopped, and both drugs can be stopped immediately.

Transplant patients who take azathioprine or 6-MP for prolonged periods of time have an increased risk of developing certain cancers. Although this is a theoretical concern, there has not been an

increased rate of these cancers in IBD patients taking these drugs.

3.2 *Cyclosporin*

Cyclosporin is a more recently developed immunosuppressive drug which has been very useful in transplantation. Consequently it was thought that it might be useful in IBD.

There have been encouraging reports of a beneficial effect in severe active ulcerative colitis. Although its effect is not yet proven, it may allow some patients who are not responding to intravenous injections of corticosteroids to avoid surgery. However, it is not yet known how long-lasting this effect will be. Unfortunately, despite initial promising reports, the balance of evidence now suggests that it is not helpful in severe Crohn's disease. It is very expensive and is usually used when other medical therapies have failed.

Cyclosporin is a relatively toxic drug with a number of side-effects, many of which are more likely when blood levels of the drug are high. Regular blood level measurements are essential. Side-effects include high blood pressure, impaired kidney function, susceptibility to infections, nausea, loss of appetite, facial hair, tremor, pins and needles or numbness of the fingers and toes, headaches, gum swelling and epileptic seizures.

3.3 *Methotrexate (Ledertrexate®, Methoblastin®)*

Methotrexate has been used in the treatment of cancer for many years. Lower doses have been used in psoriasis and more recently in rheumatoid arthritis, and there is some evidence that it may be helpful for IBD which is not responding to other drugs. Methotrexate is usually given as a weekly tablet or injection.

The most common side-effect is nausea. Methotrexate can also cause deficiency of folic acid, which is necessary for blood formation. Folic acid tablets are often prescribed with methotrexate. Other side-effects include diarrhoea, liver and lung damage. Bone marrow suppression can lead to increased susceptibility to infection.

4. **Antibiotics**

4.1 *Metronidazole (Flagyl®)*

Metronidazole is the only antibiotic with an accepted role in the treatment of IBD. Its use is confined to Crohn's disease - most commonly to control anal complications such as abscesses or fistulas. It has also been shown to have some beneficial effect in Crohn's disease at other sites, particularly the large bowel. It is not known whether the effect of metronidazole is due to its antibiotic activity (ie. its ability to kill bacteria).

The most common side-effects are nausea and loss of appetite, indigestion, a metallic taste in the mouth, diarrhoea and headache occur less frequently. Prolonged treatment with metronidazole can damage the nerves in the feet and arms, leading to tingling and numbness. This is reversible on stopping the drug but may take some months to return to normal. Some people have an unpleasant reaction to alcohol (flushing of the face, headache, palpitations, nausea, shortness of breath and drowsiness) while they are taking metronidazole. It is probably best to abstain from alcohol.

B. NON-SPECIFIC DRUGS

5. Anti-diarrhoeal Drugs

Loperamide (Imodium®, Dicap®), diphenoxylate + atropine (Lomotil®) and codeine phosphate reduce diarrhoea but have no effect on the inflammation which is causing diarrhoea. They are related to narcotic drugs such as morphine but have a much lower risk of addiction, especially loperamide and Lomotil®. They work mainly by reducing the contraction of the muscle in the bowel wall, slowing the movement of bowel contents through the gut. They also cause some reduction of the amount of fluid produced by the lining of the gut.

These drugs should not be used in children or in a severe attack of colitis, when they may cause the bowel to enlarge and burst. They can be useful to control diarrhoea during milder attacks of IBD, or in patients who have diarrhoea even though their disease is inactive. The main side-effect is constipation. Other side-effects are unusual, although probably more common with codeine phosphate than with loperamide and Lomotil®. Drowsiness, headache, mood changes and skin rashes can occur. Lomotil contains atropine, which can cause a dry

mouth, blurred vision, palpitations and difficulty passing urine, but usually only when larger amounts are consumed.

6. Bile Salt Binders

Cholestyramine (Questran®) and colestipol (Colestid®)

Bile salts are a normal component of bile which is secreted from the liver into the upper gut to aid in the absorption of food. They are normally reabsorbed in the lower part of the small bowel, the terminal ileum. However, if the terminal ileum is damaged (because of extensive Crohn's disease or surgery) bile salts pass into the large bowel and cause diarrhoea by irritating its inner lining.

Cholestyramine (Questran®) and colestipol (Colestid®) are two drugs that bind to bile salts, preventing them from causing diarrhoea. Their most frequent side-effects are constipation, abdominal discomfort and abdominal distension. Heartburn, nausea and loss of appetite can also occur. They can also interfere with absorption of food (in which case diarrhoea may be worsened) and other medications. Both are powders which are dissolved in fluid before consumption. Many patients find their taste unpleasant. The main use of these drugs is to treat high cholesterol levels.

7. Analgesics (Pain Killers)

Paracetamol (Panadol®) and paracetamol + codeine (Panadeine®)

Pain most commonly occurs during a flare-up. The best treatment is to suppress the activity of the disease using one of the specific drugs already discussed. However, it is perfectly safe to use common analgesics such as paracetamol or mixtures of paracetamol and codeine for a short time to relieve pain. It is probably best to avoid aspirin, and nonsteroidal anti-inflammatory drugs such as ibuprofen (Nurofen®) and diclofenac (Voltaren®), which can cause damage to the stomach.

A minority of IBD patients have more persistent pain. Regular analgesics can be helpful but it is important to discuss your symptoms with your doctor as this sort of pain may be caused by a complication which requires specific treatment.

8. Vitamins and Minerals

All patients with IBD need a well-balanced, nourishing diet. Vitamin and mineral supplements are generally unnecessary especially if the disease is inactive. However, there are a few exceptions.

The most important is the use of regular vitamin B₁₂ injections in some patients with Crohn's disease. Vitamin B₁₂ is essential for blood formation and for nerve and brain function. It is absorbed from the lower part of the small bowel, the terminal ileum, a common site of Crohn's disease. If there is extensive Crohn's disease of the terminal ileum or if a significant length of terminal ileum has been surgically removed vitamin B₁₂ absorption is compromised. The body has enough vitamin B₁₂ in the liver to last 3 years but eventually deficiency causes anaemia or symptoms of nerve dysfunction such as tingling of the arms and legs. Deficiency is detected by a blood test to measure vitamin B₁₂. If you develop vitamin B₁₂ deficiency you will need to have an injection of vitamin B₁₂ every 3 months for the rest of your life.

Most other vitamins and minerals are absorbed in the upper part of the small bowel which is less commonly affected by Crohn's disease. However, a few individuals with extensive disease or surgery require supplements, most commonly iron or folic acid. Iron supplements may also be necessary in patients who have bled from the bowel. Iron tablets cause the bowel motions to turn black. They can also cause indigestion and nausea. Some patients with extensive Crohn's disease absorb fat poorly, particularly if they are taking bile salt binders. They may require supplements of fat-soluble vitamins (vitamins A, D or K).

9. Unconventional Therapies

It is natural for people with a disease that cannot be cured by orthodox medicine to seek a cure elsewhere. While some alternative therapies may be harmless, or even helpful (eg. relaxation techniques, yoga and meditation, acupuncture) others may be detrimental (eg. restrictive diets) particularly if the therapists suggests that all usual medications are stopped. You should feel

free to discuss these therapies with your doctor or with representatives of the CCSG.

10. Drug Treatment and Pregnancy

Women with IBD who become pregnant are naturally concerned that their medications will be harmful to the baby. In general it is best to take as few medications as possible during pregnancy but it is important to realise that uncontrolled disease is a much greater threat to the baby than the drugs used to treat it. There is no evidence that the 5-ASA containing drugs used to prevent flare-ups (sulphasalazine, olsalazine and mesalazine) do any harm and they should not be stopped. Doctors recommend folic acid supplements during pregnancy. Bile salt binders and vitamin and mineral supplements are also perfectly safe.

Flare-ups occurring during pregnancy should be treated aggressively, usually with corticosteroids, to bring the disease under control as quickly as possible. Enemas, foams or suppositories may be safer as the amount of steroid absorbed into the body is very small.

It is probably preferable not to conceive or carry a child while taking azathioprine, but there is no evidence of an increased rate of abnormalities among children of male or female IBD patients taking this drug. There is very little information on methotrexate or cyclosporin, therefore *they should not be taken* during pregnancy. Anti-diarrhoeal agents (loperamide, Lomotil®, codeine) should be used with caution at all times. Dependence of the newborn and respiratory depression are possible side effects of these agents.

If you are concerned about taking any drugs that may be necessary for a flare-up during pregnancy, please do not hesitate to discuss any issues with your doctor and for further information refer to the CCSG Information Leaflet No.4, *Sexuality, Fertility and Pregnancy*.

CONCLUSION

This booklet describes the most common drugs which are used in the treatment of IBD. Don't be alarmed by the long list of side-effects. Most are uncommon and the majority of IBD patients have few problems with their

medications. You should consult your doctor if you have any questions about the drugs or if you are concerned about possible side-effects.