DRUG THERAPY

NSAIDS – NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

They are symptomatic anti-inflammatory, anti febrile (fever) and analgesic (pain reducing) medications. Symptomatic means that they do not affect the course of the disease, but serve to controls symptoms.

They act mainly by blocking an enzyme, which is important for the formation of substances that can cause inflammation.

On the other hand, these substances also have a physiological role in the body that includes stomach protection and regulation of blood flow in the kidney. These physiological effects explain most of the side effects of NSAIDs.

These side effects include:

Gut problems. These are the most common side effect, causing injuries to the lining of the stomach.

Symptoms range from mild abdominal discomfort after taking the medication, to severe abdominal pain and bleeding from the stomach, that may appear as black and loose stools.

Gastrointestinal side effects in children are poorly documented, but in general are considerably less of a problem than those observed in adults. NSAIDs have to be taken with food.

Side effects involving the liver can cause an increase in liver enzyme, but it is hardly of significance except with aspirin.

Kidney problems are rare and only happen in children who have had previous problems with the heart, liver or kidneys.

NSAIDs can affect blood clotting, but this is not clinically important unless the child already has a blood clotting abnormality. Aspirin is the drug that causes the most problems with blood clotting. This side effect is exploited for the treatment of diseases in which there is an increased risk of thrombosis (formation of pathologic blood clots inside the blood vessels). In this case, aspirin in low doses is the drug of choice.

Several NSAIDs are available. Naproxen and Ibuprofen are widely used. Aspirin, although cheap and effective, is less used nowadays because of its side effects. NSAIDs are not used in conjunction with one another.

Children will respond differently to different NSAID, so one NSAID may be effective were another has failed.

Recently, another category of NSAIDs has been introduced in the market, called COX-2 inhibitors (Celecoxib, Rofecoxib).

These drugs seem to have less gastric side effects than the other NSAID, whilst maintaining the same therapeutic power.

COX-2 inhibitors are much more expensive than the other NSAIDs and the debate on their relative safety and efficacy over traditional NSAIDs is not yet concluded. The experience with these drugs in children is very limited.

Cyclosporine A
Cyclosporine A is an immunosuppressive drug, initially used to prevent organ rejection in patients who underwent transplant operations. It is a potent inhibitor of a group of white blood cells that have a fundamental role in the immune response.
It can be given in liquid or pill form.
Side effects are quite frequent, especially at high doses and may limit the use of the drug. They include renal damage, high blood pressure, liver damage, gum enlargement, hair growth over the body, nausea and vomiting.
Treatment with cyclosporine, therefore, requires regular clinical and laboratory check-ups to assess these side effects.

Intravenous immunoglobulins
Intravenous immunoglobulins (IVIG) are prepared from large pools of plasma from healthy blood donors. Plasma is liquid component of human blood. IVIG are the treatment for children who lack antibodies, because of a defect in their immune system. However, through mechanisms that are still unclear and may vary in different situations, IVIG have also been shown to be helpful in some autoimmune and rheumatic diseases.
They are given by intravenous infusion and, generally, represent a safe therapy. Side effects are rare and include anaphylactoid (allergic) reactions, muscle pains, fever and headache during infusion, headache and vomiting about 24 hours after infusion, this resolves spontaneously.
IVIG are free of HIV, hepatitis and most other known viruses.

Corticosteroids
Corticosteroids (CS) are a large group of hormones that are produced by the human body. The same, or very similar, substances can be manufactured synthetically and used for the treatment of various conditions.
The steroid prescribed to children is not the same as those used by athletes to enhance performance.
CS are very potent and rapidly acting drugs, suppressing inflammation by interfering with immune reactions in quite a complex manner. They are often used to achieve more rapid clinical improvement of a patient's condition, before other treatments start to work.
Apart from their immunosuppressive and anti-inflammatory effects, they are also involved in many other processes within the body, e.g. in cardiovascular function and stress reaction, water, sugar and fat metabolism and blood pressure regulation.
There are considerable side-effects, associated mainly with long-term therapy with CS. It is very important that a child is under the care of a physician who is experienced in the management of the disease and in minimizing the side-effects of these drugs.

Dosages and ways of administration.
CS can be swallowed, or injected into a vein, or given locally by injection in to a joint or the skin).
Dose and route of administration are chosen according to the disease to be treated, as well as the severity of a patient's condition. Higher doses, especially when given by injection, are powerful and act rapidly.

Oral tablets are available in different sizes, containing different amounts of the drug. Prednisone and prednisolone are most commonly used.
There is no generally accepted rule for drug dosing and frequency of administration.
A dose taken once a day or once every other day (in the morning) has less side effects than a split dose taken at different times of the day. A split dose can be more effective and is, therefore, sometimes necessary to maintain control of the disease. In severe disease, many physicians will prefer to choose high-dose methylprednisolone, which is given as an infusion into the vein, usually once daily for several days in a row.
Sometimes, daily intravenous administration of smaller doses may be used when oral medication has not been effective.
Injection of long-acting CS into the inflamed joints is a treatment of choice in arthritis, usually triamcinolone, acetonide, or hexacetonide. These drugs have the active steroid substance bound on small crystals that, after having been injected into the joint cavity, spread around the inner joint surface and release CS over a prolonged period. This often leads to a long-term anti-inflammatory effect.
Nevertheless, duration of this effect is highly variable lasting weeks to months. One or more joints can be treated in one session using combinations of skin anaesthetic cream, or spray, local anaesthesia, sedation (midazolam, entonox), or general anaesthesia, depending on the number of joints to be treated and the age of the patient.

Side effects
There are two main types of side effects that occur with CS: those resulting from prolonged use of large doses and those resulting from withdrawal of therapy. If CS are taken continuously for more than about one month they cannot be stopped suddenly as this might cause severe problems. This is because the body will stop producing the steroids naturally during treatment and, if corticosteroids are stopped suddenly, the body can take months to begin producing the steroids in the amounts needed to maintain normal health.
The efficacy, as well as the type and severity of CS side effects, are individual and are difficult to predict. The side effects usually relate to the dose and administration regimen, e.g. the same total dose would have more side effects if given in divided daily doses rather than in a single morning dose.
The main visible side effects include, increased hunger, which is difficult to control and can result in weight gain and the development of stretch marks on the skin. Keeping a well-balanced diet, low in fat and sugars and high in fibre, will help to control weight gain.
Acne on the face can be controlled by skin treatment. Problems with sleeping and mood changes, with feelings of being jittery or shaky, are common. With long-term CS treatment growth is often suppressed.
Defence against infections may also be altered, resulting in more frequent, or severe, infections depending on the extent of immunosuppression. Chickenpox may run a serious course in immunosuppressed children, so it is very important to alert your doctor immediately when your child either develops the first signs, or you realise that he or she has been in close contact with someone who subsequently develops the disease.
According to the individual situation injection of antibodies against chickenpox virus, or anti-viral antibiotic can be given.

Most of the less obvious side effects may be revealed by close monitoring during treatment. They include, loss of bone mineral, causing the bones to become weaker, making the patient more prone to fractures (osteoporosis).
Osteoporosis can be identified and followed by a special technique called bone densitometry. It is believed that a sufficient supply of calcium (about 1000 mg daily) and vitamin D may be useful to slow down the evolution of osteoporosis.
Side effects involving the eye include cataract and glaucoma. If increased blood pressure evolves, a low-salt diet is important. Blood sugar levels can raise causing steroid-induced diabetes, this is when a diet low in free sugars and fat is necessary.

AZATHIOPRINE
Azathioprine is a medication that decreases immunity.
It works by interfering with the production of DNA, a process that all cells need in order to divide. The inhibition of the immune function is, in fact, due to the effect of the drug on the growth of one kind of white blood cells (lymphocytes.)
It is administered orally. Although usually better tolerated than cyclophosphamide, it can have some side effects that need close monitoring.
Gastrointestinal problems (oral ulcers, nausea, vomiting, diarrhea, epigastric pain) are uncommon. Liver toxicity may occur, but is rare. A reduction in the number of circulating white blood cells (leukopenia) may occur and is dose related. The reduction in the number of platelets, or red blood cells, is less comon.
The long term use of azathioprine may be associated with an increased risk of cancer, but so far the evidence is not conclusive.
As with other immunosuppressive agents, treatment exposes the patient to an increased risk of infections. Herpes zoster infection, in particular, is observed with higher frequency in patients treated with azathioprine.

Cyclophosphamide
Cyclophosphamide is an immunosupressive medication, which reduces inflammation and suppresses the immune system. It works by interfering with the multiplication of cells, altering the synthesis of DNA. It is particularly active on those cells such as blood cells, hairs and intestinal lining cells that multiply at a high rate.
White blood cells, called lymphocytes, are affected the most by cyclophosphamide and their change in function and number explains the suppression of the immune response. Cyclophosphamide has been introduced to treat certain forms of cancer. In rheumatological diseases, when it is used in intermittent therapy (given as a monthly injection) it has fewer side effects than in cancer patients.
Cyclophosphamide is administered orally, or intravenously. In this latter case, huge doses are usually given at four weekly intervals.
Cyclophosphamide is a drug that greatly reduces immunity and has several side effects that need close laboratory monitoring. The most common are nausea and vomiting. Reversible thinning of the hair can also occur.
Excessive reduction in the number of circulating white blood cells, or platelets, may occur and may need dose adjustment or temporary withdrawal of the drug.
Bladder problems may occur, but is much more common in patients on a daily oral dose, rather than those on monthly injections. To avoid this problem, plenty of water should be

drunk.
Long term treatments run the risk of fertility impairment and increased cancer frequency, depending on the cumulative dose of the drug taken by the patient.
Cyclophosphamide reduces the immune defences and therefore increases the risk of infections, especially, if given in association with other agents that interfere with immunity, such as high dose corticosteroids.

Methotrexate
Methotrexate (MTX) is a drug used in children with a number of different diseases for many years. It was initially developed as a anti-cancer drug because of its ability to slow down the rate of the cell division.
Nevertheless, this effect is only significant in higher doses. In low intermittent doses, used in rheumatic diseases, MTX reaches its anti-inflammatory effect through other mechanisms. When used in such small doses, the majority of the side effects seen with larger doses do not occur, or are easy to monitor and manage.
MTX is available in two main forms, tablets and as an injection. It is given only once weekly, on the same day of the week.
The physician decides on the route of administration and dose according to the individual patient's condition.
Tablets are better absorbed when taken before a meal and, preferably, with water. Injections can be administered just under the skin, but can also be given into the muscle or vein.
Injections have the advantage of better absorption and less stomach problems. MTX therapy is usually long-term. Most of the physicians recommend treatment to continue for at least 6-12 months after symptoms subside.
Most children on MTX have very few side effects. They include nausea and stomach upset. These can be managed by taking the dose at night. A vitamin, called folic acid, is often prescribed to prevent these side effects.
Using anti-sickness drugs before and after the MTX dose, or changing to the injected form, can help. Other side effects include mouth ulcers and skin rash.
Coughs and breathing problem are rare side effects in children. The effect on the number of blood cells, if present, is usually very mild. Long term liver damage appears to be very rare in children, because other liver toxins, such as alcohol, are not a problem.
Usually, MTX therapy is interrupted when liver enzymes increase and re-started when they fall back to normal.
Regular blood tests are therefore needed during MTX therapy.
Although a risk of infections is usually not increased in children treated with MTX, some of them may have a more serious course.
Among these, chickenpox, or shingles, seems to be of importance. If your child has not had chicken-pox but comes in contact with someone who develops it or if your child develops chickenpox you should contact your physician immediately as a special medication may be needed.
If your child is a teenager other considerations may become important. They include alcohol intake which should be strictly avoided as it may increase the liver toxicity of MTX. MTX may harm an unborn baby so it is very important that contraceptive precautions are taken when a young person becomes sexually active.

Hydroxychloroquine
Hydroxychloroquine was originally used for the treatment of malaria. It has been shown to interfere with several processes related to inflammation.
It is given as a once daily tablet and is usually well tolerated. Gastrointestinal problems may occur, but are not severe. The main concern is toxicity to the eye. Hydroxychloroquine accumulates in the retina and persists for long period of time after treatment has been discontinued.
These alterations are rare but may cause blindness even after medication has been stopped. However, this eye problem is extremely rare at the low doses currently used.
Early detection of this complication prevents visual loss if medication is discontinued. Periodic eye examinations are necessary, although there is a debate about the need and frequency of these controls when hydroxychloroquine is administered at low doses.

Sulfasalazine
Sulfasalazine is a combination of an antibacterial and an anti-inflammatory drug. It was conceived many years ago when adult rheumatoid arthritis was thought to be an infectious disease. Despite the rational for its use subsequently being revealed to be wrong, sulfasalazine has been shown to be effective in some forms of arthritis as well as in a group of diseases characterized by chronic gut inflammation.
Sulfasalazine is administered orally. Side effects are not uncommon and require periodic blood tests.
They include gastrointestinal problems (anorexia, nausea, vomiting diarrhoea), allergy with skin rash, liver problems, a reduced number of circulating blood cells and a decrease in serum immunoglobulin concentrations.
This drug should never be given to systemic Juvenile Idiopathic Arthritis, or Juvenile Systemic Lupus Erythematosus patients, because it can induce severe flares of these diseases.

Colchicine
Colchicine has been used for centuries. It inhibits the function and numbers of white blood cells, blocking inflammation.
It is given orally. Most of the side effects are related to the gastrointestinal system. Diarrhea, nausea, vomiting and occasional abdominal cramps may improve with a lactose-free diet. These side effects usually respond to a short term dose reduction.
After the disappearance of these signs, an attempt to slowly increase the dose to the original level can be made. There might be a decrease in the number of blood cells, therefore, periodic tests for blood cells counts are required.
Muscle weakness may be seen in patients with renal or liver problems. Prompt recovery is achieved after discontinuation of the drug.
Another side effect is damageto the peripheral nerves (neuropathy), and, in these rare cases, the recovery may be slower.
Rash and alopecia may also be observed occasionally.
Serious intoxication may occur after ingestion of high amounts of the drug. The treatment of colchicine intoxication requires medical intervention. Gradual recovery is usually

observed, but sometimes it may be fatal. Parents should be very cautious that the drug is not within the reach of small children.
Colchinine treatment in Familial Mediterranean Fever is continued throughout pregnancy. If there are additional risks factors an amniocenthesis in the third to fourth month of the pregnancy (testing for abnormal chromosomes from a small sample obtained from the fluid surrounding the baby) should be performed.

Anti – TNF agents
Tumor necrosis factor (TNF) is a molecule that plays a central role in the inflammatory process. Thanks to modern biotechnology different type of medications that selectively inhibit TNF have been produced.
These include antibodies against TNF (infliximab and adalimubab) and TNF receptor blockers (etanercept).
Etanercept is administered by a subcutaneous injection. Patients, as well as family members, can be taught to self-administer these injections. Local reactions (red spot, itching, swelling) may occur at the site of injection. These reactions are usually of short duration and mild intensity.
Infliximab is administered intravenously in a hospital setting. During the infusion an allergic reaction may occur going from mild reaction (shortness of breath, red skin rash, itching) that are easily treated, to serious allergic reactions with hypotension (lowering of the blood pressure) and the risk for shock.
These allergic reactions occur most frequently after the first infusion and are due to an immunization against a portion of the molecule. If an allergic reaction occurs, the drug is withdrawn.
Adalimubab is the same as infliximab and is administered by a subcutaneous injection.
All these drugs have a potent anti-inflammatory effect that persists as long as they are administered. Side effect are mainly represented by a greater susceptibility to infections, especially tuberculosis.
Evidence of serious infectious should lead to drug withdrawal. In some rare instances treatment has been associated with the development of autoimmune diseases other than arthritis.
Since the experience with TNF-inhibitors is recent, long term safety data is still lacking.
These therapies are frequently referred to as biological agents, because they are produced by biotechnologies.
There are other such agents like IL1ra and IL6 antibodies that are being used in the treatment of some adult rheumatic diseases and, experimentally, in children.
All biological agents are very expensive.