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Drug Therapy

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1. NSAIDs – Non-Steroidal Anti-Inflammatory Drugs

1.1 Description

Non-steroidal anti-inflammatory drugs (NSAIDs) have traditionally been the main treatment for many paediatric rheumatic diseases. Their role remains important and most children are prescribed NSAIDs. They are symptomatic, anti-inflammatory, anti-febrile (antipyretic) and anti-pain (analgesic) medications; symptomatic means that they do not clearly affect the course of the disease, they might have limited effects on the progression of the disease as described in adults with rheumatoid arthritis, but they can control symptoms due to inflammation.
They act mainly by blocking an enzyme (cyclooxygenase) that is important for the formation of substances that can cause inflammation, called prostaglandins. These substances also have a physiological role in the body that includes stomach protection, regulation of blood flow in the kidneys, etc. These physiological effects explain most of the side effects of NSAIDs (see below). Aspirin was widely used in the past because it is cheap and effective, while today it is used less due to its side effects. The most widely used NSAIDs are naproxen, ibuprofen and indomethacin.
More recently, new generations of NSAIDs, known as cyclooxygenase (COX)-2 inhibitors, have been made available, but only a few have been studied in children (meloxicam and celecoxib). Even so, there is still no widespread use of these substances in children. These drugs seem to have less gastric side effects than other NSAIDs while maintaining the same therapeutic power. COX-2 inhibitors are more expensive than the other NSAIDs and the debate over their safety and efficacy compared to traditional NSAIDs is not yet concluded. Experience with COX-2

inhibitors in paediatric patients is limited. Meloxicam and celecoxib have proven to be effective and safe in children in a controlled trial. There are differences in the response of children to different NSAIDs, so one NSAID may be effective where another has failed.

1.2 Dosage/modes of administration

A 4 to 6 week trial of a single NSAID is necessary to assess its efficacy. However, since NSAIDs are not disease-modifying drugs (i.e. they are not able to modify the course of the disease), they are used more to treat pain, stiffness and fever associated with systemic arthritis. They can be given in liquid or tablet form.

Only a few NSAIDs are approved for use in children: the most common are naproxen, ibuprofen, indomethacin, meloxicam and celecoxib.

Naproxen

Naproxen is administered at 10-20 mg per kg per day in 2 doses.

Ibuprofen

Ibuprofen is administered in children from 6 months to 12 years at a typical dose of 30 to 40 mg/kg/day in 3 to 4 divided doses. Children normally start at the lower end of the dosing range and then gradually increase the dose as needed. Children with milder disease may be treated with 20 mg/kg/day; doses greater than 40 mg/kg/day may increase the risk of serious adverse effects; doses greater than 50 mg/kg/day have not been studied and are not recommended. The maximum dose is 2.4 g/day.

Indomethacin

Indomethacin is administered in 2- to 14-year-olds at 2 to 3 mg/kg/day given in 2-4 divided doses. The dose is titrated upward to a maximum of 4 mg/kg/day or 200 mg per day. It should be given with food or immediately after meals to reduce gastric irritation.

Meloxicam

Meloxicam is administered in children greater than or equal to 2 years of age at 0.125 mg/kg orally once daily with a maximum dose of 7.5 mg orally daily. There is no additional benefit demonstrated by increasing the dose above 0.125 mg/kg once daily in clinical trials.

Celecoxib

Celecoxib is administered in children 2 years or older: 10 to less than or equal to 25 kg at a dosage of 50 mg orally twice daily; for children greater than 25 kg, the dosage is 100 mg orally twice daily.

Interactions between different NSAIDs are not indicated.

1.3 Side effects

NSAIDs are usually well tolerated and side effects are less common than in adults. Gut alterations 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 toxicity of NSAIDs in children is poorly documented, but in general it is considerably less than that observed in adults. However, parents and patients should be advised to always take the medication with food to minimize the risk of gastric upset. The utility of antacids, histamine2-receptor antagonists, misoprostol and proton pump inhibitors for prophylaxis against serious NSAID-induced gastrointestinal complications in children with chronic arthritis is unclear and no official recommendations exist. Side effects on the liver can cause an increase in liver enzymes but it is of negligible significance, except in the case of aspirin.
Kidney problems are rare and only occur in children who have previous dysfunctions of the kidneys, heart or liver.
In patients with systemic JIA, NSAIDs (as other medications) may trigger macrophage activation syndrome, a sometimes life-threatening activation of the immune system.
NSAIDs can affect blood clotting but this response is not clinically significant except in children who already have a blood clotting abnormality. Aspirin is the drug that causes more clotting problems; this effect is exploited for the treatment of diseases in which there is an increased risk of thrombosis (formation of pathologic blood clots inside the vessels); in this case, aspirin in low doses is the drug of choice.
Indomethacin can be useful to control fever in resistant children with systemic juvenile idiopathic arthritis.

1.4 Main paediatric rheumatic diseases indications

NSAIDs may be used in all paediatric rheumatic diseases.