

# SIDE EFFECTS OF NON-STEROIDAL ANTI INFLAMMATORY DRUGS – NSAIDS

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## INTRODUCTION

NSAIDs are amongst the most widely used of all therapies worldwide. At this time there are more than fifty different NSAIDs available, excluding aspirin and paracetamol. They are used for the reduction of pain, inflammation and fever. There are no significant differences in their main pharmacological actions, but there are marked differences in toxicity, and important differences in individual patient's reaction to them.

A basic understanding of their pharmacology and mode of action is necessary to understand these side effects.

## PHARMACOLOGY

The Cyclo-oxygenase enzyme system (COX) plays a pivotal role in normal and abnormal physiology. There are two COX enzymes, COX -1 and COX-2. (Recent work has proposed the existence of a third type, COX-3).

COX-1 is an enzyme present in most tissues including blood platelets. It is a 'housekeeping' enzyme involved in tissue homeostasis. Inhibition of this enzyme is generally instantaneous and competitively reversible (aspirin is qualitatively different).

COX-2 is induced in inflammatory cells and produces the mediators of inflammation. The effects of inhibition of COX-2 increase with time.

The broad range of the COXs as homeostatic and inflammatory enzymes results from the wide variety of lipid metabolites that are derived from their activity. They are called PROSTANOIDS and they have important regulatory activities in the cardiovascular system, the gastrointestinal and reproductive tracts, and in the development of pain, fever and inflammation.

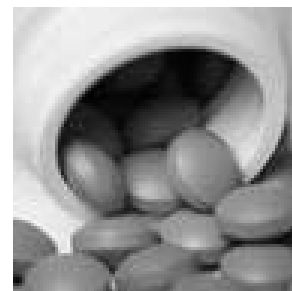
## SIDE EFFECTS (SE) OF NSAIDs

Prostanoids are responsible for the adverse effects of NSAIDs.

Numerous adverse effects from these drugs have been identified and their inherent toxicity must be considered when using them. This is especially important in the elderly and in patients with established gastrointestinal (GIT), liver, kidney, spleen, blood and bone marrow conditions.

The most commonly seen side effects (SE) resulting from inhibition of COX-1 by 'traditional' NSAIDs are shown in this table:

Ibuprofen	lowest incidence of SE, drug of first choice
Fenbufen	less risk of GIT, more risk skin reactions
Naproxen	more potent than Ibuprofen, moderate risk of SE
Mefenamic acid	skin reactions, diarrhoea likely, haemolytic anaemia reported
Nabumetone	adverse effects less marked, good anti pyretic
Diclofenac	moderate risk GIT SE
Sulindac	moderate risk of SE.
Indomethacin	high incidence SE (non GIT), headache and dizziness
Tolmetin	moderate risk SE
Piroxicam	high incidence GIT, tinnitus, rashes
Etodalac/ Meloxicam	fewer GIT SE than preceding drugs



## ASPIRIN

Absorption of Aspirin in the stomach is incomplete, most occurs in the ileum. When aspirin is broken down in the liver, other tissues and plasma, salicylates are produced. High dose (>150mg daily) and chronic therapy with Aspirin can produce local and systemic SE - tinnitus, dizziness, vertigo, and sometimes nausea and vomiting. Salicylate poisoning is a serious condition causing hyperventilation and depression of the respiratory centre, and disruption of haemostasis.

## PARACETAMOL

Widely used but is a weak anti-inflammatory. Allergic skin reactions can occur; chronic high doses may cause kidney damage.

Traditional NSAIDs such as ibuprofen, indomethacin, nabumetone and aspirin inhibit both COX-1 and COX-2. The degree of selectivity for these two enzymes is associated with the occurrence of side effects - especially gastrointestinal. In an attempt to lessen the gastrointestinal side effects whilst retaining the therapeutic benefits COX-2s were developed. The first of these were Rofecoxib and Celecoxib. In September 2004, Rofecoxib was withdrawn after being associated with thrombotic events.

COX-2 inhibitor drugs must now carry a warning that their use could be associated with cardiovascular events, heart attack and stroke. It is at this time unclear if the adverse findings for COX-2 are also relevant for the conventional COX-1 inhibitors; this is because of the lack of trials data

NSAID's are valuable drugs but must be used with caution in the elderly, and those with pre-existing conditions.

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