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EVIDENCE BASED UPDATE ON NSAIDS: OVERVIEW

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ABSTRACT

NSAIDs have a more significant effect on pain resulting from the increased peripheral sensitization that occurs during inflammation and leads nociceptors to respond to stimuli that are normally painless. The goal of this paper is to review current literature on history, mechanisms of action, efficacy, and tolerability of OTC analgesics (NSAIDS). Relatively new and potential future indications for these drugs are also discussed. Literature search was performed in January 2012 in the following electronic database: Medline, Ebsco, Pubmed, Dove Press, Bentham Publishers, and the Cochrane Library. We collected literature from 1968 to January 2012, search terms were as follows; complication, use, prevention and mechanisms of NSAIDs. This review has enlighten the pharmacological basis for the common therapeutic approaches to pain management and also elucidate the diagnosis of acute and chronic exposure of NSAIDs poisoned patients. The article briefly describe about the classification, clinical features, diagnosis, pathogenesis, fatal dose, autopsy features and management of the NSAIDs poisoning. Finally, we touch on prevention and newer therapy that might be effective in the near future.

Key words: Classification, Dose, Diagnosis, Ulcer, and Prevention.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) with knowledge and care; inappropriate prescribing may puts patients unnecessarily at risk of morbidity and mortality. There are many different NSAIDs available for prescription in India [Table .1]. It is the sixth most widely sold drugs in the world [Figure.1]. Over $6.5 billion is spent annually on NSAIDs in the United States, and over 111 million prescriptions are filled [1]. A Bleeding and perforated gastroduodenal ulcers are among the most serious complications of NSAID therapy and may lead to significant morbidity, mortality, and financial costs. Among chronic NSAID users, the annual incidence of serious NSAID-related ulcers requiring treatment and hospitalization is estimated at 1% to 2%, with an associated mortality rate of 10% to 15% [2]. The large number of drugs and formulations makes it difficult for the primary care physician to choose the best drug for his/her patient. The choice can be markedly simplified by a review of the published evidence on effectiveness and safety and by taking into consideration the cost of the drug. Health care reform and escalating health care costs make the evaluation of resource utilization increasingly important. Although knowledge about clinical endpoints is important, the process of care and the costs associated with the use of NSAIDs and Coxibs is also relevant to physicians, patients [Figure.3]. Although the gastrointestinal side-effects of chronic NSAID use, in particular gastric and duodenal ulceration, are well-documented, they are a less significant feature of acute toxicity [3,4] ; there has only been one previous report of perforated peptic ulceration associated with a mixed mefenamic acid and aspirin overdose [5] and this case had other potential confounding factors.

COX exists in at least two isoforms with similar molecular weights. COX-1 is a constitutive enzyme present in a variety of cells and tissues. The other form, COX-2, is undetectable in most mammalian tissues, but the expression of this isoform can be induced by such pro-inflammatory agents as cytokines and endotoxin. Both isoforms catalyze a cyclooxygenase reaction in which arachidonic acid is converted to PGG2 and a peroxidise reaction in which PGG2 is reduced to PGH2. Despite the enzymatic similarities between the two isoforms, there are subtle differences between their affinities toward the established NSAIDs [6]. Therefore, goal of this paper is to review current literature on history, mechanisms of action,

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efficacy, and tolerability of OTC analgesics (NSAIDS). Relatively new and potential future indications for these drugs are also discussed.

FATAL DOSE : Highly variable (4 to 40g)

DIAGNOSIS

Past/Present Medical/ Medication history of the patient.

Laboratory findings of the patient (ie) Anion-gap acidosis

Ferric chloride test

Obtain a baseline CBC, renal and liver function tests and urine analysis in symptomatic patients. After 24 hours, a red discoloration of the urine may be seen due to rubazonic acid a pyrazolone metabolite.

CLINICAL FEATURES [7]

System	Signs
Gastrointestinal	Loss of appetite, vomiting, blood vomiting, abdominal pain, diarrhea, melena (black tarry stool), superficial erosion, hemorrhage, ulceration, perforation, and inflammation,
Renal	Reduced renal flow, reduced glomerular filtration rate, fluid and sodium retention, hyperkalemia, azotemia, acute renal insufficiency, papillary necrosis.
Hepatic	Increase in liver enzymes, Jaundice
Hemostatic.	Decreased blood clotting, increased bleeding time
Hematopoietic	Bone marrow depression, aplastic anemia, hemolytic anemia, thrombocytopenia, neutropenia, pancytopenia, methemoglobinemia
Immune system	Allergic reaction
CNS	Depression, Seizure, Coma.

MECHANISMS OF ACTION

A. Anti-inflammatory effects

NSAIDs exert their anti-inflammatory effect through inhibition of prostaglandin G/H synthase, or cyclooxygenase, which is the enzyme catalyzing the transformation of arachidonic acid to prostaglandins and thromboxanes [8]. This enzyme has two recognized forms: Cox-1 and Cox-2. Selective inhibition of Cox-2 leads to decreased GI side effects. Recent work suggests that activation of endothelial cells and expression of cell adhesion molecules play a role in targeting circulating cells to inflammatory sites. NSAIDs may inhibit expression of these cell adhesion molecules and may directly inhibit activation and function of neutrophils

B. Analgesic effects

NSAIDs have a more significant effect on pain resulting from the increased peripheral sensitization that occurs during inflammation and leads nociceptors to respond to stimuli that are normally painless. In particular, it is believed that inflammation leads to a lowering of the response threshold of polymodal nociceptors .

C. Antipyretic effects

NSAIDs exert their antipyretic effect by inhibition of prostaglandin E2 (PGE2) synthesis, which is responsible for triggering the hypothalamus to increase body temperature during inflammation [9].

USES

- It is widely used to treat patients with rheumatoid arthritis and osetoarthritis. [10]
- It's used in the treatment of acute musculoskeletal injuries, and there is evidence for their ability to provide symptomatic relief of conditions such as acute low back pain [11].
- NSAIDs can help reduce fever and are also often used to treat mild to moderate pain due to a variety of conditions, such as backaches, bursitis, dental procedures, headaches, muscle spasms, premenstrual cramps, sprains, and tendinitis [12]

COMPLICATION

These includes acute tubular necrosis, acute tubulointerstitial nephritis, glomerulonephritis, renal papillary necrosis, chronic renal failure, salt and water retention, hypertension, hyperkalaemia and hypoaldosteronism. [13]

PATHOGENESIS

NSAIDs is strongly limited by their GI side effects which range in both severity and frequency from relatively mild to more serious and potentially life threatening case, such as GI ulceration and hemorrhage [14]. It is a well accepted fact that the GI side effect of acidic NSAIDs is a result of two different mechanisms [15-17].

a) Local Effect on GI Tract

The first mechanism involves a local action comprising of a direct contact effect and an indirect effect on the GI mucosa [14-17]. The direct effect can be attributed to the local inhibition of prostaglandin (PG) synthesis in the GI tract. The indirect effect can be attributed to a combination of an ion-trapping mechanism of NSAIDs in mucosal cells and back diffusion of H+ ions from the lumen into the mucosa. Topical irritation by the free carboxylic group of the NSAIDs is considered an important factor in establishing superficial stomach erosion, particularly in the corpus region of the stomach.

c) NSAIDs induced Ulcer disease

In 1960s Davenport suggested that aspirin could directly damage the gastric epithelium. The breaking of the `barrier' permitted the back-diffusion of acid into the mucosa, which eventually led to the rupture of mucosal blood vessels. These topical irritant properties were

subsequently found to be predominantly associated with those NSAIDs with a carboxylic acid residue. The unionized forms of these drugs can enter epithelial cells in the stomach and duodenum. Once in the neutral intra-cellular environment, the drugs are converted to an ionized state and cannot diffuse out. This has been referred to as `ion trapping'. As the drug accumulates within the epithelial cell, the osmotic movement of water into the cell results in swelling of the epithelial cell, eventually to the point of lysis. [18]

Another mechanism by which NSAIDs could damage the gastroduodenal epithelium is via the uncoupling of oxidative phosphorylation in the epithelial cells. Various NSAIDs have been shown to uncouple mitochondrial respiration, leading to a depletion of ATP and therefore a reduced ability to regulate normal cellular functions, such as the maintenance of intracellular pH. The ability of NSAIDs to uncouple oxidative phosphorylation also appears to be related to some extent to acidic moieties (such as carboxylic acid residues), since substitution at these sites interferes with the ability of these compounds to act as uncouplers. The theory that NSAIDs cause topical injury by virtue of their effects on mitochondrial respiration has been challenged, mainly based on the observation that gastric and duodenal ulcers are observed following the parenteral or rectal administration of NSAIDs [19,20]. Erosions and ulcers can also be produced in experimental circumstances in which NSAIDs are administered parenterally [21]. It is also difficult to comprehend how the uncoupling of oxidative phosphorylation would occur in gastrointestinal epithelial cells but not in the numerous other cells with which an NSAID would have contact subsequent to its absorption. On the other hand, the small intestine would be repeatedly exposed to NSAIDs that are excreted in bile and recycled enterohepatically, so it is conceivable that the uncoupling of oxidative phosphorylation is an important component of the pathogenesis of NSAID-induced enteropathy.

A third mechanism that could account for the topical irritant properties of NSAIDs is their ability to decrease the hydrophobicity of the mucus gel layer in the stomach. Lichtenberger and co-workers have proposed that this layer is a primary barrier to acid-induced damage in the stomach.[22,23] They demonstrated that the surface of the stomach is hydrophobic and that this hydrophobicity can be reduced by various pharmacological agents. For example, NSAIDs were shown to associate with the surface-active phospholipids within the mucus gel layer, thereby reducing its hydrophobic properties. These investigators further demonstrated that the mucus gel layer in the stomach of rats and mice given NSAIDs was converted from a non-wettable to a wettable state. This effect was found to persist for several weeks or months after the cessation of NSAIDs administration.[24-26]

b) Systemic Effects

The second mechanism is based on the generalized systemic action occurring after absorption and can be manifested even after intravenous dosing [27,28]. The systemic effects are manifested due to inhibition of synthesis of gastric PGs like PGI2 and PGE2.

TREATMENT

Stomach wash may be beneficial up < 2 hours after ingestion, since toxic doses of NSAIDs often cause mucosal ulcer in the stomach

Activated charcoal (AC): It is said to be very efficacious in the treatment of NSAIDs poisoning since each gram of AC can adsorb 550mg of the drug.

Ipecac induced emesis is not recommended because of the potential for CNS depression and seizures.

Treat convulsions in the usual manner.(ie) benzodiazepines

Urinary alkalinisation: Alkalinisation of both blood and urine can be achieved with intravenous sodium bicarbonate.It is postulated that the excretion of phenylbutazone, like salicylate, may be enhanced in an alkaline urine. This may be considered in very severely intoxicated patients. However, alkaline diuresis is of questionable value since pyrazoles are extensively metabolized and only 1% to 5% of the drug is eliminated unchanged by the kidneys [18].

Haemoperfusion in life-threatening cases. Because of the low water solubility and high protein binding, haemodialysis is not likely to be effective. Plasmapheresis is claimed to be beneficial in severe poisoning and has been tried successfully in a case of phenylbutazone overdose.

Graham DY et al 2002 reported that frequency of serious events like bleeding and perforations were less, bleeding reduced by 40% and overall reduction was 60-70%. However, the side effects like diarrhoea were the limiting factors. Several randomised trials have shown that the proton pump inhibitor drugs such as omeprazole are effective in reducing gastrointestinal damage caused by NSAIDs if they are given prophylactically [29].

Celecoxib and rofecoxib have especially become popular among clinicians. COX-2 inhibitors have been developed with the contention that inhibition of constitutive COX-1 by non-selective NSAIDs is responsible for the side effects such as ulcer and bleed. Therefore, drugs that spare this isoform should be free from these side effects. Short-term and long-term studies of patients taking these drugs have confirmed this notion. Incidence of serious side effects has been found to be comparable to placebo, while the incidence is 20-40% with conventional non-selective drugs. Two main prospective trials of COX-2 inhibitors involving about 8,000 patients each such as celecoxib and rofecoxib long-term arthritis safety study (CLASS) and VIGOR (vioxx gastrointestinal outcome research study) suggest that these have superior tolerability, safety, and in some cases efficacy as well over conventional NSAIDs. [30]

Newer therapy of NSAIDS (Locofelone) has a diplomatic action on competitive, COX-2 cyclooxygenase and 5-lipooxygenase blocker. The rationale of its development represents the simple application of pharmacological principles in newer therapeutics. It is well known that cyclooxygenase enzyme has two isoforms upon which NSAIDs act, i.e., COX-1 and COX-2. Conventional NSAIDs and COX-2 selective inhibitors act mainly on COX-2. Blockade of COX-2 enzyme by COX-2

inhibitors leaves the COX-1 isoform unchecked and this contributes to enhanced thrombogenicity in the patients. Blockade of both COX-1 and COX-2 isoforms leads to increased formation of products of 5-lipooxygenase pathways and hence gastric mucosal damage take place in stomach. Locofelone acts to inhibit both isoforms (COX-1, COX-2) and 5-lipooxygenase. However, it improved safety profile compared to other NSAIDs is believed to be due to its unique mechanism of action [31].

PREVENTION

- ❖ Use single NSAIDs drug
- ❖ Use the lowest possible doses
- ❖ Use for short durations
- ❖ Use less gastrotoxic drugs like paracetamol, ibuprofen, and diclofenac
- ❖ Use selective COX-2 inhibitors wherever possible and especially in high risk cases
- ❖ Review drug use especially in elderly rheumatoid arthritis and Osteo arthritis patients
- ❖ Avoid concomitant gastrotoxic drugs like steroids
- ❖ Consider prophylaxis with omeprazole in high risk cases
- ❖ Have a high index of suspicion on GI symptoms in NSAIDs users
- ❖ Educate patients against non-prescription use; counsel them about the warning symptoms of gastro intestinal damage such as blood stained stools, blood in vomitus, and etc.

AUTOPSY FEATURES

Autopsy studies revealed that 8.4% of regular NSAIDs consumers had ulcers in jejunum or ileum . Erosions of gastric mucosa. Black, altered blood may lie in the stomach. Sometimes massed concretions of tablets are present. Although non-steroidal anti-inflammatory drug-induced colopathy is well described, colonic perforations complicating non-steroidal anti-inflammatory drug intake are rare. Researcher reported a patient with rheumatoid arthritis who was on long-term diclofenac and presented with early colonic stricture formation and a caecal perforation, which to the best of our knowledge, has only been reported once before. It is important to suspect this diagnosis in patients on non-steroidal anti-inflammatory drug therapy who present with an acute abdomen. [20] [Figure 2].

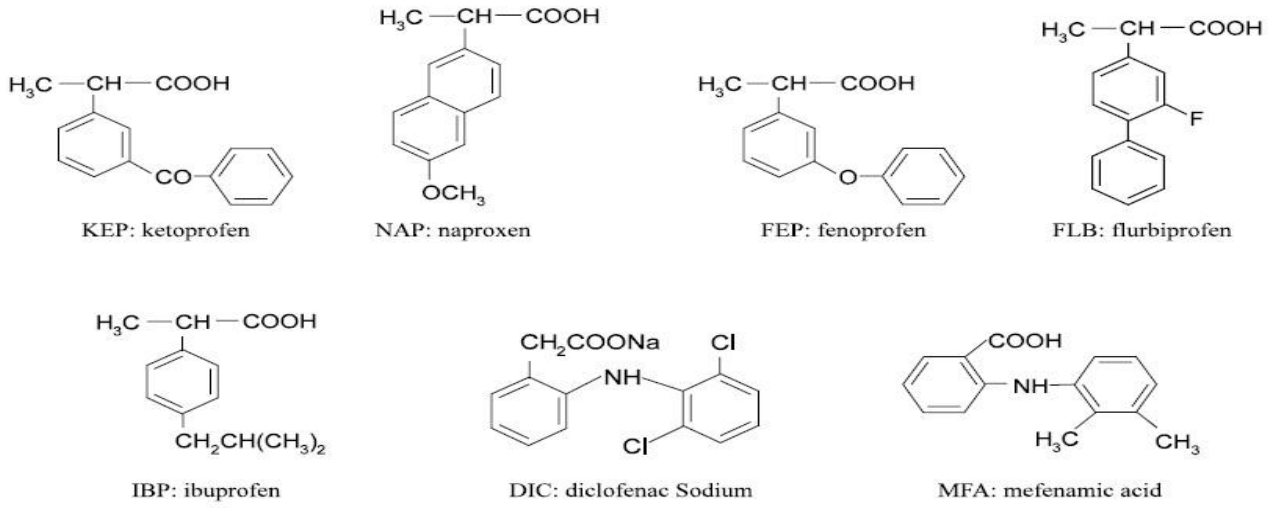


Fig. 1. Chemical structures and abbreviations of NSAIDs studied.

Figure 2. Haematoxylin and eosin stain (×20) demonstrating deep ulceration (arrow) through the muscle close to the site of perforation with overlying peritonitis

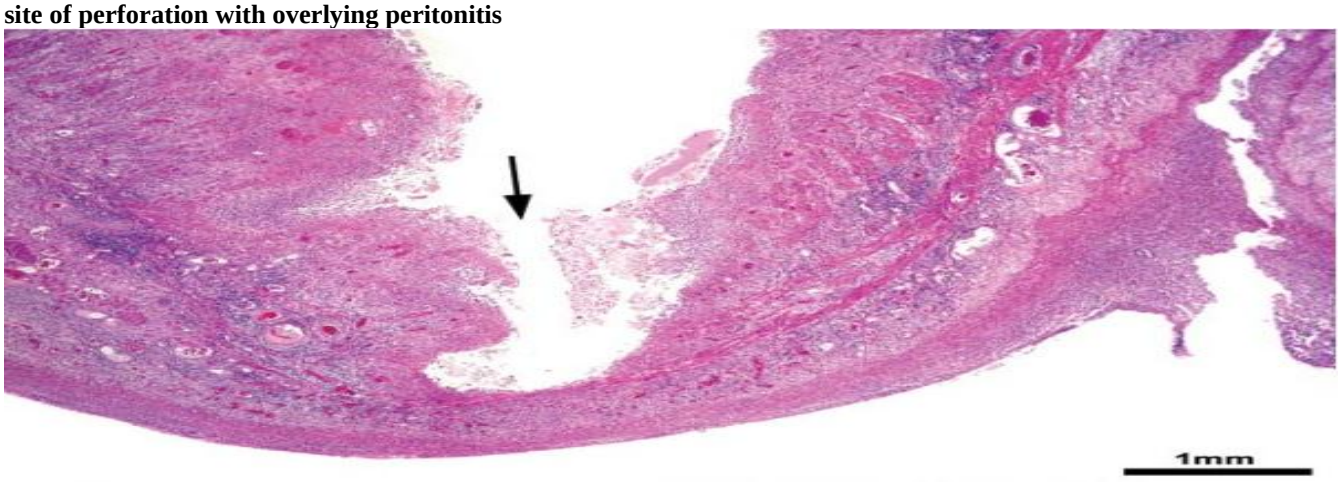
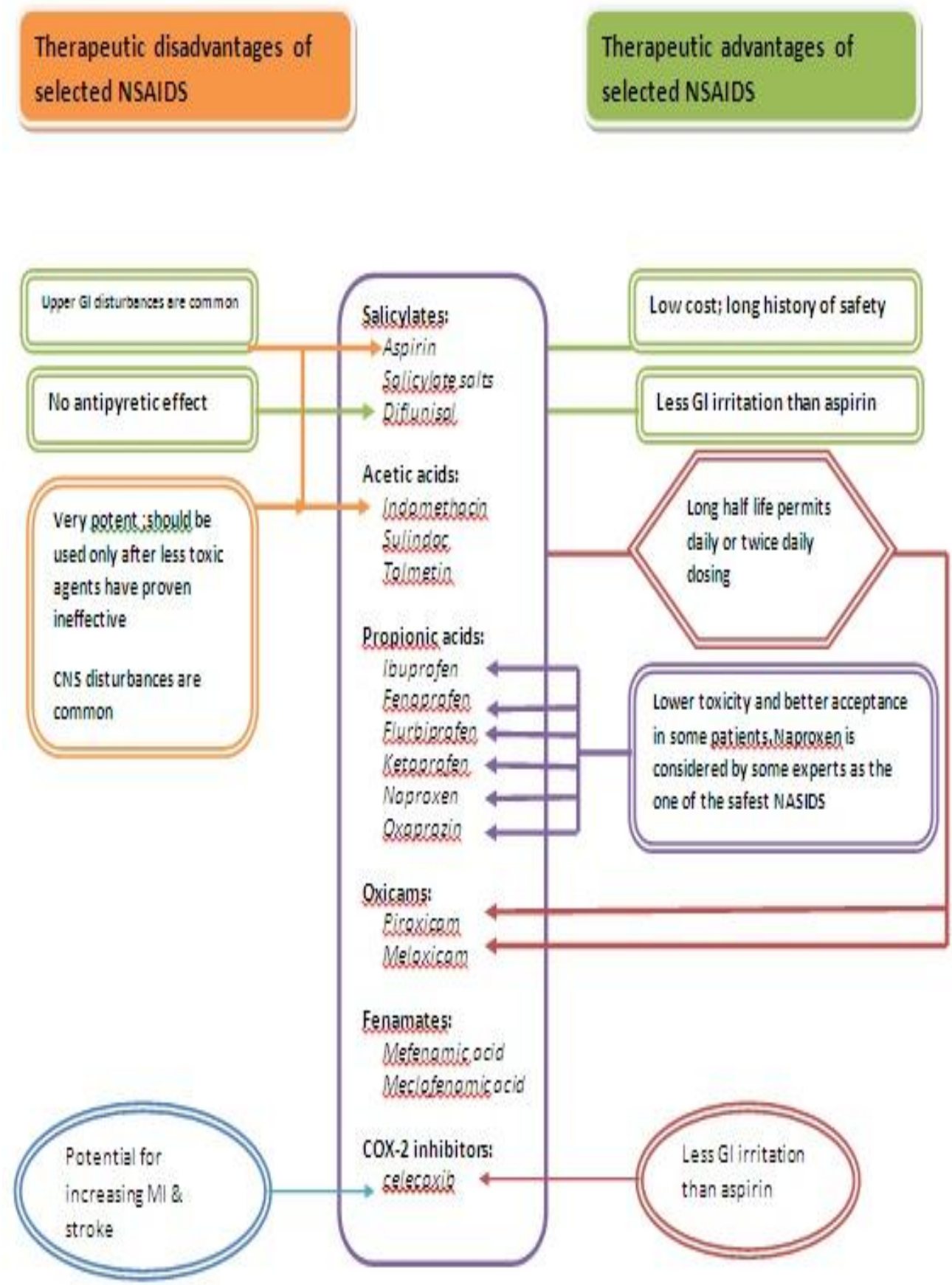


Figure 3. Advantage and disadvantage of selected NSAIDs



The NSAIDS, sometimes called the aspirin-like drugs, are among the most widely used of all drugs. There are now more than 50 different NSAIDS on the global market; some of the more important examples are listed in Table.1 . Comparison of some common non-steroidal anti-inflammatory drugs and coxibs

Classification	Major toxic effect	Generic Name	Type	Recommended dose	Half-life (Hrs)	Proprietary name	RD	Gout	MS	PO	Dys	H&M	Comments
P-aminophenol derivatives	Hepatic function impairment	Aceclofenac	Phenylacetate	100mg,bid	2-4	Acecol	+						-
Salicylate	High incidence of peptic ulcers: blood dyskrasias; Hypersensitivity	Aspirin	Salicylate	1200-1500mg, tid	2-19	Ecotrin	+		+	+	+	+	Mainly cardiovascular usage
		Diflunisal			2-19	Dolobid	+		+	+	+		-
Heteroaryl acetic acid		Ketorolac	Pyrrolizine	10mg,qid	4-10	Cadolac (IV/Tab)	+			+			-
Acetic acid derivatives	Gastric irritation	Sulindac	Indene	150-200mg,bid	8	Clinoril	+	+	+				Prodrug
		Diclofenac	Phenylacetate	50-75mg,qid	1.1	Voltaren	+	+	+	+			Moderate potency
		Etodolac	Pyroanocarboxylate	200-300mg,qid	6.5	Lodine	+						Possibly fewer gastrointestinal effects
		Indometacin	Indole	50-70mg,tid	4-5	Microcid	+	+	+		+		Suitable for moderate to severe disease
		Acemetacin		60mg	1	Rantudil Forte (c)	+		+	+			Ester of indomethacin
Arylpropionic acid derivative	Gastric irritation, hepatic function impairment	Ketoprofen	Propionate	70mg.tid	1.8	Rhofennid	+	+	+	+	+		Suitable for mild disease
		Naproxen		375mg,bid	14	Artagen		+	+		+		-
		Dexketoprofen		25-100mg	1-4	Actidex				+	+		-
		Fenbufen		900mg	10	Toyond	+		+				-
		Fenoprofen		600mg,qid	2.5	Nalfon	+		+				Prodrug activated in liver
		Flurbiprofen		300mg,tid	3.8	Flurofen (T)	+		+	+	+	+	-
		Ibuprofen		600mg,tid	2	Brufen (T)	+		+	+	+	+	Suitable for children
		Tiaprofenicacid		300mg,bid	3-6	Surgam	+		+				-
Anthranilic acids	Gastric irritation, hepatic function impairment ,peptic ulcers.	Mefenamic acid	Fenamate	500mg,tid	3-4	Mefacid (S/Tab)	+		+	+	+		Moderate activity
		Tolfenamic acid		200mg	6.5	Clotan (C)						+	-
Enolic acids	High incidence of peptic ulcers;hypersensitivity	Meloxicam	Oxicam	7.5-15mg,qd	20	Rafree (Tab)	+						Possibly fewer gastrointestinal effects
		Piroxicam		20mg,qd	5-7	Pirox (T/C/IV)	+	+	+				-
		Tenoxicam		20mg		Tobitil (T)	+		+				-
Alkanones	High incidence of peptic ulcers	Nabumetone	Napthylalkenone	1000-2000mg, qd	26	Nabuflam (Tab)	+						Prodrug activated in liver
Cox-2inhibitors	Gastric irritation; hypersensitivity	Parecoxib	Coxib	20-80mg	8	Praxis (Vial)	+			+			Prodrug activated in liver
		Etoricoxib		60mg	22	Coxia	+	+					-
		Celecoxib		100-200mg,bid	11	Celebrax	+						Fewer gastrointestinal effects

Dys; Dysmenorrhoea; H&M- Headache and Migraine; MS- Musculoskeletal disorders; PO- Postoperative Pain; RD-Rheumatic diseases (e.g. rheumatoid arthritis and osteoarthritis). (From British Medical Association and Royal Pharmaceutical Society of Great Britian 2005, British National Formulary, BMA and RPSGB.

CONCLUSION

This review has enlighted the pharmacological basis for the common therapeutic approaches to pain management and also elucidate the diagnosis of acute and chronic exposure of NSAIDs poisoned patients. The article briefly describe about the classification, clinical features, diagnosis, pathogenesis, fatal dose, autopsy features and management of the NSAIDs poisoning. Finally, we touch on prevention and newer therapy that might be effective in the near future.

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