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Ibuprofen pharmacology and its implications for musculoskeletal disorders

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Introduction

The goals of pain management in orthopedics are to provide pain relief and to facilitate rehabilitation and a return to normal function. Given the many, heterogeneous diseases in this field, we have preferred, in this review, to distinguish between acute and chronic conditions, briefly describing each disease and the relative literature on the applications of ibuprofen.
Non-steroidal anti-inflammatory drugs, particularly ibuprofen, are commonly used in clinical practice, and since the 1970s, authors have been trying to clarify their role, i.e. the precise indications, dosages, and levels of efficacy, in each of the most common musculoskeletal diseases. Unfortunately, this issue remains controversial for many reasons. Indeed, the quality of some manuscripts, the small number of patients included in some studies, genetic differences between populations, failure to clarify the precise physiopathology of many inflammatory/degenerative musculoskeletal diseases, commercial interests of companies, and the high cost of randomised studies have all contributed to the confusion.

The pharmacology of NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are a heterogeneous group of compounds with analgesic, antipyretic and anti-inflammatory properties and they are among the most commonly prescribed drugs in the treatment of several musculoskeletal diseases, such as rheumatoid arthritis, osteoarthritis, synovial inflammation and musculoskeletal injuries (1,2).
These effects are presumed to result from inhibition of a key step in the synthesis of prostaglandins, i.e. the conversion of arachidonic acid to prostaglandin H2, which is catalysed by the enzyme cyclo-oxygenase (COX) (3,4). Prostaglandins are produced in several cells types and therefore play different roles in normal homeostasis. They are produced in platelets and gastric mucosal cells through the constitutively expressed COX-1 isoenzyme and are involved in physiological functions, e.g. the functional integrity of gastrointestinal and renal tracts, and platelet function. Instead, the inducible COX-2 isoenzyme is involved in the regulation of platelet activity and in the inflammatory response under the influence of noxious stimuli. However, it has been demonstrated that the COX-2 enzyme is also constitutively expressed in healthy human tissues such as gastric mucosa (5,6).
The discovery of two different COX enzyme subtypes (COX-1 and COX-2) led to a new classification of NSAIDs based on their potential selectivity of action (7) and prompted a further increase in their differential therapeutic applications.
In particular, NSAIDs may be divided into: i) traditional NSAIDs, which include COX-1 selective (aspirin and salicylates) inhibitors and COX-1/COX-2 non-selective inhibitors (e.g. ibuprofen) (Table I) and ii) COX-2 selective inhibitors (coxibs).
However, acetaminophen, a para-aminophenol derivative, posed a problem with regard to this classification, as it has analgesic and antipyretic actions but little or no anti-inflammatory activity (8); this led to the suggestion, several years ago, that there is a further COX in the brain, named COX-3 (4). To date, however, the existence of the putative COX-3 has not been proven, the presence of a COX-1 variant seeming more likely, even though the presence of another COX gene has not been ruled out (9).
The ability of NSAIDs to inhibit both COX-1 and COX-2 may increase the efficacy of this class of drugs. Indeed, when the lipoxin pathway is activated in the presence of COX-1 inhibitors, acetylation of the COX-2 enzyme oc-

Table I - Classification of traditional NSAIDs by COX-1/COX-2 ratio

NSAIDS	COX-1/COX-2 ratio
Piroxicam	250
Aspirin	166
Ibuprofen	15
Flurbiprofen	1.3
Meloxicam	0.8
Naproxen	0.6

curs to inhibit further production of prostanoids through arachidonic acid metabolism while inducing the synthesis of 15-R-hyroxy-(p)-eicosatetraenoic acid that is transformed into 5(6)-epoxytetraene, and then into 15-epi-lipoxins or into aspirin-triggered 15-epi-lipoxins (ATLs). Both 15-epi-lipoxins and ATLs control the resolution phase of acute inflammation and promote lesion healing (10,11) The generation of lipoxins or ATLs triggered by "first-phase" proinflammatory lipid mediators may explain the potentially serious cardiovascular consequences of the chronic use of selective COX-2 antagonists (see later). Inflammation is a multifactorial process, therefore a single "paninflammatory" agent cannot antagonise all the deleterious pathways involved while preserving the resolution pathways (12).

As such, COX-2 selective inhibitors (e.g., rofecoxib, valdecoxib, and celecoxib) could induce a prolongation of the resolution of inflammation. Although inhibition of the COX-2 pathway through use of these NSAIDs may attenuate acute inflammatory effects, the corresponding reduction in lipid mediators, such as PGE2, would fail to generate the proresolving lipoxins that are required for restoring homeostasis in tissues (13). The resulting chronic low-grade inflammation may also explain findings of increased myocardial risk in individuals receiving long-term treatment with selective COX-2 inhibitors (14).

The NSAIDs approved by the US Food and Drug Administration (FDA) as over-the-counter (OTC) analgesics can be separated into three groups: salicylates (e.g. aspirin, salycilic acid, diflunisal), proprionic acid derivatives (e.g. ibuprofen, naproxen, and ketoprofen) and the para-aminophenol derivative acetaminophen.

Ibuprofen, a 2-proprionic derivative, is a balanced COX-1/COX-2 inhibitor and is able to induce reversible binding to the COX-active sites.

Ibuprofen was derived from proprionic acid in studies conducted by the research arm of the British Boots Group during the 1960s (15). Discovered by Andrew R.M. Dunlop, Stewart Adams, John Nicholson, Jeff Wilson and Colin Burrows, it was patented in 1961 and introduced into the UK in 1969; subsequently, in the 1970s, it was introduced worldwide as a prescription-only medication, recommended at doses of up to 2400 mg/day for the treatment of musculoskeletal pain and inflammation, as well as for other pain conditions (16). In the 1970s, it was often prescribed either as a first-line NSAID or in place of aspirin, indomethacin or phenylbutazone for the treatment of arthritic conditions, on account of its good efficacy and lower gastrointestinal adverse effects. Moreover, it has been documented that ibuprofen is also able to reduce cartilage and synovial tissue degradation and therefore represents a good treatment in patients with osteoarthritis (17).

Ibuprofen exists as a racemic mixture of both R(-) and S(+) enantiomers. It has been estimated that between 50 and 60% of R(-) ibuprofen undergoes stereospecific inversion to S(+) ibuprofen (18,19).

The anti-inflammatory and perhaps analgesic activities of ibuprofen (determined by COX inhibition) are thought to lie almost exclusively with the S(+) enantiomer (20,21).

More recent studies showed that the anti-platelet effect of ibuprofen was related to the plasma unbound concentration of S(+) ibuprofen (22). Furthermore, the S(+) enantiomer is an effective analgesic for patients with rheumatoid arthritis (19).

By contrast, R(-) ibuprofen is less active as a prostaglandin synthesis inhibitor but has shown some pharmacological properties relevant to the anti-inflammatory actions of ibuprofen (23). However, 50-60% of the R(-) form of ibuprofen is metabolically converted to the S(+) form in the intestinal tract and liver after oral absorption (24).

Although the anti-inflammatory and analgesic properties of NSAIDs result primarily from the inhibition of the formation of prostaglandins, by blocking COX activity at the site of tissue injury (25), thereby preventing the sensitising activity of prostaglandins at nociceptive nerve endings (26), these drugs might have other, independent effects. In fact, Nielsen et al. (27) in a clinical trial supposed that ibuprofen could also act centrally on prostaglandin release or have a direct effect on peripheral nerve endings (28).

Moreover, it has been demonstrated in experimental studies that several NSAIDs, such as ibuprofen, ketorolac, and flurbiprofen, are able to inhibit the fatty acid amide hydrolase (FAAH), the enzyme that degrades anandamide (29,30), thus leading to increased anandamide, palmitoylethanolamide (PEA) and oleoylethanolamide levels. It has been demonstrated in the formalin test that the combination of ibuprofen with anandamide produced a synergistic analgesic effect mediated by CB1 and partially by CB2 cannabinoid receptors (31). Indeed, this modulation of the endogenous cannabinoids, by blocking their degradation enzymes (FAAH), conferred a better antinociceptive effect than endocannabinoids given alone (32).

Absorption and distribution

Ibuprofen is rapidly absorbed from the upper gastrointestinal tract (Tmax <0.25 hours for granules and about two hours for tablets), although absorption is delayed if ibuprofen is administered with food (33). The plasma S/R ratio is dependent on the time-release characteristics of the formulation, higher ratios being obtained with sustained-release as opposed to immediate-release formulations.

Like most other NSAIDs, ibuprofen has a half-life of 2.1 hours (Table II) which, even should repeat administra-

Table II - Half-lives of NSAIDs in healthy patients

Drug	Half-life (h)
Aspirin	0.2
Diclofenac	1.1
Ketoprofen	1.8
Ibuprofen	2.1
Flurbiprofen	3.8
Ketorolac	5.1
Naproxen	14
Celecoxib	16
Piroxicam	57

tion be required, is able to reduce the development of side effects (see later).
Ibuprofen and the other NSAIDs tend to have similarly small values for total body clearance (0.01 to 0.05 L/kg/min) and volume of distribution (10 to 15 L for an individual weighing 70 kg), and extensive binding to plasma proteins (90 to 99%; except for acetaminophen which is approximately 20% bound) (34-36).
However, as we will discuss below, the binding to plasma proteins differs between ibuprofen and other NSAIDs (e.g. aspirin) and this could explain the different drug-drug interaction during NSAID treatment in a patient on polytherapy.
Protein binding is a major determinant of the distribution of an NSAID. It is likely that free drug approaches an equilibrium across the synovium. Therefore, at the steady-state the free-drug concentrations of salicylates (37) and ibuprofen (38) are the same on both sides of the synovial membrane. Although in inflammatory joint diseases the albumin-bound drug diffuses better across the membrane, because of the increased capillary permeability to proteins, total NSAID concentrations at the steady state are lower in synovial fluid than concurrent concentrations in plasma. This could also be related to the lower albumin concentrations in synovial fluid with respect to plasma (ratio range 0.54 to 0.8) (39).
However, the concentrations of NSAIDs in synovial fluid are able to reduce the inflammatory pattern in chronic inflammatory diseases. In fact, the ratio of total ibuprofen concentrations in the synovial fluid to those in plasma is about 1.24 at 7 h following a single, 600 mg dose of the drug and 0.52-1.46 at 3-12 h after three daily doses of ibuprofen 1.8 g/day (40). The mean free total ibuprofen in synovial fluid ranges from 1.81 to 2.91% compared with that in plasma, which is 1.54-2.53%. Thus, appreciable levels of total and free R-/S-ibuprofen accumulate in the synovial fluid of arthritic patients and clearly this will have therapeutic significance as regards the local anti-inflammatory and analgesic effects of the drug in pain control. Moreover, synovial fluid accumulation of R(-) and S(+) enantiomers shown a broad peak plasma levels at about 2-4 h, thereafter extending to about 12-15 h (41).
However, similar data have been produced with other NSAIDs; indeed, in a patient with RA, a high ketoprofen concentration in the synovial fluid was documented and found to be able to inhibit prostaglandin E2 levels in synovial fluid (39). Moreover, Bruno and coworkers (42) reported, in synovial fluid of 407 outpatients with active osteoarthritis treated with naproxen sodium 1100 mg, high concentration of naproxen with a synovial half-life of 31±12 hours.

Metabolism and excretion

Like other NSAIDs, ibuprofen is extensively metabolised in the liver, principally through cytochromes e P450 2C9 (CYP-2C9), CYP-2C8 and 2C19 participating in the oxidation of the alkyl side chain to hydroxyl and carboxyl derivatives.
Impaired liver metabolism in patients with moderate to severe cirrhosis leads to prolongation of the t1/2 to 3.1 h and 3.4 h for R(-) and S(+) ibuprofen with evidence of reduced metabolic inversion of the R(-) to S(+) enantiomer (43). Alcoholic liver disease also prolongs both the Tmax and the half life (44).
Phase II metabolism involves formation of phenolic and acyl glucuronides (45) and a minor route of conjugation with taurine, which is stereospecific to the S(+) enantiomer because of formation from the thioester CoA which participates in the R(-) to S(+) conversion (46).
Biliary excretion in humans of unchanged drug and active phase II metabolites accounts for about 1% of the drug, which compares with the 50% accounted for by urinary excretion (47). The 15 known UDP-gluronyltransferases that catalyse the formation of glucuronides in human liver have been shown to be controlled by five UGTIA and five UGT2B genes (48).
Ibuprofen shows linear kinetics up to 1200 mg, therefore, within this dosage, the elimination is not saturable. Moreover, due to its very short half-life (2.1 hours), the presence of liver or renal disease does not increase significantly the plasma area under the curve (AUC) of ibuprofen and therefore the use of ibuprofen is associated with very low side effects.
Moreover, a correlation has also been reported between dose and the area under the blood concentration-time curve, and there is indeed a high AUC for the high dose; this dose-serum concentration relationship of ibuprofen was similar regardless of whether it was given in the form of granules or tablets (Fig. 1a and Fig.1b) (49).
It is also important to underline that the pharmacokinetic parameters of ibuprofen in children <12 years old can be considered similar to those of young and middle-aged adults (Cmax: 35.8 mcg/mL; Tmax: 1 to 2 hours; volume distribution: 0.22 to 0.27 L/kg; half-life 0.9 to 2.3 hours; drug plasma clearance 80 to 110 mL/h/kg; metabolism: CYP2C9 and 2C8).

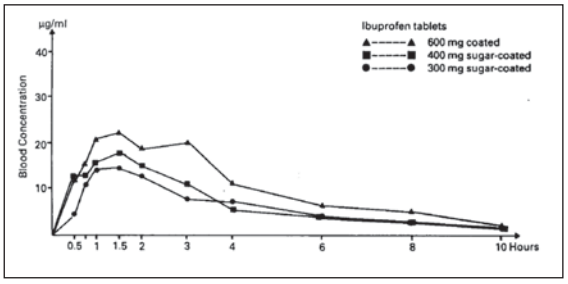

Figure 1a - Mean plasmatic curves of ibuprofen after single doses of coated tablets (49)

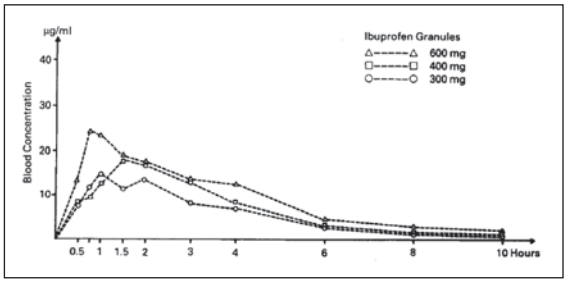

Figure 1b - Mean plasmatic curves of ibuprofen after single doses of granules (49)

Clinical implications

Acute musculoskeletal diseases

Paediatric fractures

Paediatric fractures may be the most common of the paediatric pain conditions. It has been estimated that by the age of 15 years, between a half and two-thirds of children will have sustained a fracture (50), but it seems that children receive analgesics less frequently than adults (51). No standard of care exists for the pain management of acute musculoskeletal injury in children and adolescents. There are few studies in the literature that examine the use of common oral painkillers, and paediatric patients often do not receive adequate analgesia. Most paediatric fractures are managed at home and are therefore fractures requiring effective and well-tolerated oral analgesia. Ibuprofen and acetaminophen with codeine are the medications most commonly prescribed and used for the treatment of paediatric outpatients affected by fractures. Drendel et al. recently found no significant differences in satisfaction or functional outcomes between both medications, but more adverse effects in children treated with acetaminophen with codeine (52). Clark et al., in a 2007 randomised controlled trial, compared acetaminophen, ibuprofen and codeine for the treatment of pain in children with acute musculoskeletal injury in the emergency department. They administered a single oral dose of 15 mg/kg of acetaminophen, or 10 mg/kg of ibuprofen or 1 mg/kg of codeine to three groups of children with acute musculoskeletal injury. Patients treated with ibuprofen had significantly greater improvement in pain score after 1 hour than those treated with acetaminophen or codeine; also, at the same timepoint, more patients in the ibuprofen group, compared with the other two groups, achieved adequate analgesia. They also noted that ibuprofen resulted in significantly better improvement of pain in fracture patients at 60 and 120 minutes (53).

Koller et al., in a 2007 prospective, randomised, double-blind study comparing ibuprofen vs ibuprofen plus oxycodone in 66 (28 fractures) paediatric patients with mild-to-moderate orthopaedic injuries, found no differences in pain relief between the two groups, but more adverse effects in the group treated with ibuprofen plus oxicodone (54).

In 2009, Friday et al. compared ibuprofen and acetaminophen with codeine for the management of acute mild to moderate traumatic musculoskeletal pain in paediatric patients. They administered acetaminophen-codeine (1 mg/kg as codeine, maximum 60 mg) or ibuprofen (10 mg/kg, maximum 400 mg/kg) orally to patients from 5 to 17 years of age with an isolated extremity injury. Both painkillers provided measurable analgesia with minimal adverse effects and similar performance in terms of analgesic effectiveness (55).

Recently Drendel et al. randomised 336 children aged 4 to 18 years with arm fractures to a suspension of either ibuprofen (10 mg/kg) or acetaminophen with codeine (1 mg/kg codeine component per dose). The authors did not find any case of delayed healing, non-union or increased rate of refracture in composed fractures. Children receiving ibuprofen had significantly fewer adverse effects than children treated with acetaminophen with codeine (Table III).

The authors concluded that ibuprofen should be the first-choice painkiller for acute paediatric arm fractures (56).

Currently, paediatric clinical trial data show that ibuprofen is at least as effective as acetaminophen with codeine and codeine alone and that ibuprofen has an adverse effect profile similar to or better than those of the oral opioids to which it has been compared (57).

Adult fractures

Adult fracture care is, today, an enormous unresolved socioeconomic problem worldwide; osteoporosis, road accidents and sports injuries seem to be the main causes. NSAIDs are commonly used to treat fracture pain. There is evidence from basic science that NSAIDs inhibit bone formation, bone metabolism and fracture healing (58-61). In a case-control study, Giannoudis et al. investigated NSAID use in 99 patients with intramedullary-nailed femoral shaft fractures and found an association between the use of NSAIDs after fracture and non-union or delayed healing (62). Another database analysis assessed prescription NSAID and opioid use in 10,000 patients with humeral shaft fractures. Patients using NSAIDs within 90 days of the fracture had a 3.7-fold risk of non-union, while the risk among opioid users was 1.6-fold (63). Despite previous clinical data, Adolphson et al. found no difference between piroxicam and placebo on recovery or on bone density in 42 postmenopausal women with displaced Colles' fractures (64).

Unfortunately, fracture healing outcome is influenced by many factors, for example the complexity of the fracture, surgical procedures, associated diseases, smoking, genetic behaviour and others. Generally the use of NSAIDs is not recommended in the long-term treatment of fractures, but there is no evidence that a single dose of ibuprofen or short-term use of the drug purely for analgesic purposes is associated with delayed fracture healing in humans. A double-blind, randomised study on fracture healing outcome and NSAIDs assumption is greatly needed (65).

Table III - Percentage of children reporting adverse events comparing ibuprofen vs acetaminophen with codein group

Adverse Effect	Acetaminophen With Codeine, %	Ibuprofen, %	Difference, % (95% CI)
Any effect (n=234)	50.9	29.5	21.4 (9.1 to 33.7)
Nausea (n=231)	18.0	5.0	13 (4.8 to 21.1)
Vomiting (n=230)	11.0	2.4	8 (2.0-15.0)
Drowsy (n=231)	30.6	20.8	9.8 (–1.4 to 21)
Dizzy (n=231)	5.4	2.5	2.9 (–2.1 to 8.0)
Constipation	1.7	2.5	–0.7 (–4.3 to 3.0)
Other (n=232)	10.8	6.6	4.1 (3.1 to 11.4)

Low back pain

Low back pain (LBP) is a common musculoskeletal disorder. Pain and discomfort are localised below the costal margin and above the inferior gluteal folds, with or without leg pain. The lifetime prevalence of LBP is reported to be over 70% in industrialised countries (one-year prevalence 15% to 45%, adult incidence 5% per year) and 26% of adult Americans report pain of at least one day's duration every three months. The peak prevalence occurs between the ages of 35 and 55 (66,67). Acute LBP is usually self-limiting (recovery rate 90% within six weeks). Pengel et al. showed that most people with acute uncomplicated LBP have rapid improvements in pain and disability within one month (68), but 2%-7% of people develop chronic pain, a problem that accounts for 75%-85% of total workers' absenteeism (66). LBP can be classified by the duration of the symptoms: acute (less than 4 weeks), sub-acute (4-12 weeks), chronic (more than 12 weeks). Worldwide, NSAIDs are the drugs most frequently prescribed and most widely used for patients with LBP. Two systematic meta-analyses found strong evidence that NSAIDs relieve pain. Koes and colleagues analysed 26 randomised trials and stated that NSAIDs might be effective for short-term symptomatic relief in patients with uncomplicated LBP, but are less effective or ineffective in patients with sciatica and with nerve root symptoms (69). Van Tulder also found no differences in pain relief with ibuprofen 600 mg compared to nimesulide (70). The last Cochrane review, including 65 trials, concluded that NSAIDs are effective for short-term symptomatic relief in patients with acute LBP without sciatica, and that there does not seem to be a specific type of NSAID that is clearly more effective than the others (71). Recently, guidelines for the management of LBP in primary care recommended the prescription of NSAIDs as a useful option for symptomatic relief in the management of acute non-specific LBP (72-75). Maybe there is a need for better-designed studies to clarify which of the NSAIDs is best in the management of acute LBP.

Ankle sprains

Ankle injuries are the most common sports and recreational injuries, accounting for 38% to 45% of such injuries (76). In 2001, 2.6 million people in North America received treatment for foot and ankle injuries (77). Inadequately treated pain associated with ankle sprain may prevent patients from quickly returning to their normal activities, including work and sports activities. More than 40% of ankle sprains can progress to chronic problems (78). Numerous clinical studies have evaluated the effects of NSAIDs in acute and chronic soft-tissue injuries. McLatchie et al., in 1985, reported that patients receiving ibuprofen 2400 mg/day after grade 1 or 2 ankle sprain had less tenderness 7 days after injury and were able to achieve a higher level of training than those who received placebo (79). Dupont et al., in 1987, published a double-blind study comparing ibuprofen at a dose of 2400 mg per day and a placebo in the first week of treatment of 61 acute ankle sprains of varying degrees of severity. The authors did not find statistically significant differences between groups, although there emerged trends indicating a superiority of effectiveness in the ibuprofen group (80). Fredberg et al., in 1989, found discordant results with respect to above study using the same dose of ibuprofen (2400 mg/day) in patients with acute ankle sprain (81). Ogilvie-Harris et al., in 1995, suggested that NSAIDs shortened the time to recovery after ankle soft tissue injuries and were associated with less pain (82). Dalton et al., in 2006, published a multicentre, randomised, double-blind study, comparing acetaminophen extended-release and ibuprofen for treatment of the signs and symptoms of grade I or II lateral ankle sprains. Patients were randomly assigned to receive either acetaminophen extended release 3900 mg daily (1300 mg every 8 hours) or ibuprofen 1200 mg daily (400 mg every 8 hours). The authors found no statistical differences in the outcome of the two groups with no significant adverse drug reactions (83).

Ligament and tendon injuries

Approximately 95,000 new cases of acute rupture of the anterior cruciate ligament occur annually in the United States, and approximately 50,000 of those are reconstructed each year. Instead, the incidence of Achilles tendon ruptures and other acute ligament and tendon disorders in the general population is difficult to determine (84). The effects of NSAIDs on soft-tissue healing are not as clear-cut as those on bone healing. Vogel, in 1977, reported that administration of acetylsalicylic acid, indomethacin, or phenylbutazone in rats increased collagen deposition as well as the strength of physeal cartilage, skin, and tendon and of granulomas induced by implantation of glass rods (85). Tissue culture studies show decreased collagen synthesis with naproxen and indomethacin but increased synthesis with aceclofenac (86).

A study of injured ligaments in the rat showed a 32% lower load to failure in a group treated with celecoxib (87).

Studies of ligament healing in animal models have shown no effect from using ibuprofen (88). Recently, an *in vitro* investigation of the effect of ibuprofen on rat Achilles tendon cells showed no effect on mRNA and protein expressions of types I and III collagen, while the expression of collagenases including MMP-1, -8, -9, and -13 was upregulated (89). It was recently shown that indomethacin and celecoxib seem to impair rotator cuff tendon-to bone healing (90).

In all, the results are inconclusive and more studies are needed to determine the effects that NSAIDs and COX-2 inhibitors might have on tendon and ligament healing in sports-related injuries (91).

Dahl et al., in 2004, compared the analgesic properties of ibuprofen and acetaminophen, given separately or together after arthroscopically-assisted anterior cruciate ligament reconstruction in 61 patients randomised into three groups: 1000 mg of acetaminophen, 800 mg of ibuprofen, or a combination of 1000 mg acetaminophen and 800 mg of ibuprofen. They found that ibuprofen 800 mg thrice daily after arthroscopically-assisted anterior cruciate ligament reconstruction under general anaesthesia had better analgesic effects than acetaminophen 1000 mg thrice daily (Fig. 2). Both ibuprofen and the ibuprofen-acetaminophen combination reduced pain and was opioid sparing. The authors concluded that the use of NSAIDs in the perioperative period is beneficial and opioid sparing, thus reducing unwanted side effects of opioids, such as nausea, vomiting, drowsiness and respiratory depression, and that 800 mg of ibuprofen thrice daily as a basic oral analgesia is efficacious and well tolerated (92).

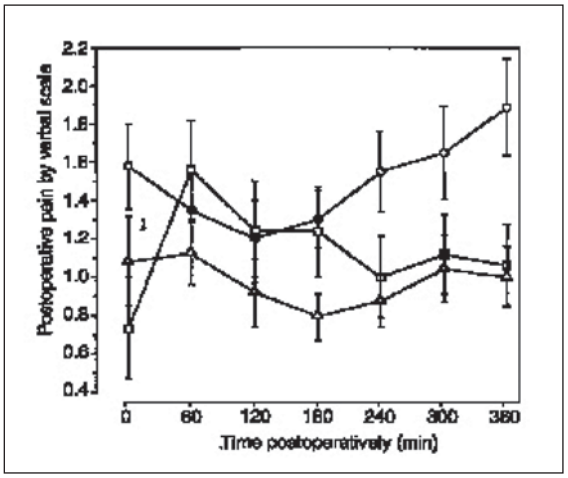

Figure 2 - Mean pain the first postoperatively as estimated by the VAS and verbal scale. The acetaminophen group had significantly more pain than the two other groups ($P < 0.05$). –o–: acetaminophen; –□–ibuprofen; –△– ibuprofen + acetaminophen.

Judicious use of NSAIDs may be more appropriate in the management of acute ligament sprains, muscle strains, tendinopathy, and eccentric muscle injury. However, the treatment duration should always be kept as short as possible, taking into account the specific type of injury, and the level of dysfunction and pain (93).

Delayed-onset muscle soreness

Delayed onset muscle soreness (DOMS) is an uncomfortable experience both for the elite athlete and for the novice. Symptoms can range from muscle tenderness to severe debilitating pain. Eccentric contractions (muscle lengthening) have been demonstrated to result in relatively large amounts of muscle damage and soreness. Hasson et al. reported that prophylactic ibuprofen (400 mg initiated 4 h before collection of baseline data and strenuous eccentric exercise bout) and therapeutic ibuprofen (400 mg initiated 24 h after baseline) similarly reduced levels of perceived muscle soreness 24 and 48 h after high-intensity eccentric exercise (94). Trappe et al., in 2001, studied the influence of ibuprofen and acetaminophen on skeletal muscle protein fractional synthesis rate and muscle soreness. They administered ibuprofen 400 mg thrice daily (total of 1200 mg) or 4000 mg daily divided into three administrations, or the same number of placebo pills. They found that ibuprofen and acetaminophen reduced the synthesis of muscular protein after high-intensity eccentric resistance exercise. The long-term influence of this acute response after resistance exercise in individuals who chronically consume NSAIDs was not determined in this study (95). More recently Tokmakidis et al. published a report on the effects of ibuprofen on DOMS, indirect markers of muscle damage and muscular performance. Patients performed eccentric leg curl exercise to induce muscle soreness in the hamstrings. Than they were randomised to two groups and took ibuprofen 400 mg every 8 hours for 48 hours or a placebo. The results of this study showed that ibuprofen can decrease muscle soreness induced after eccentric exercise but cannot assist in restoring muscle function (96). Piroxicam did not provide any notable benefit in healing experimental muscle strains (97). Long-term use of NSAIDs may inhibit the normal hypertrophic response to resistance training and future studies on the impact of chronic consumption of OTC doses of these drugs on skeletal muscle are warranted.

Postoperative pain management

Orthopaedic procedures may induce more intense pain than do other surgical procedures because bone injury is more painful than soft-tissue injury. This is due to the periosteum having the lowest pain threshold of the deep somatic structures (98). In two separate studies involving more than 10,000 patients in Canada and Sweden, patients who had undergone orthopaedic surgery had the most intense pain of all patients who had undergone ambulatory surgery (99). One study implied that orthopaedic surgeons undertreat pain, especially after shoulder surgery, operations for hardware removal, and elbow arthroscopy (100). Moreover, severe postoperative pain is a common reason for delays in hospital discharge and unanticipated hospital admissions, while effective pain relief can lead to an earlier return to work and to psychological benefits (101). NSAIDs have analgesic and opioid-sparing effects, and they have been shown to reduce the postoperative opioid consumption after major orthopaedic surgery. Ibuprofen and acetaminophen seem to have equivalent analgesic efficacy, but overall NSAIDs seem to be superior for postoperative pain management. However, there have emerged differences, depending on the type of surgery, in the levels of efficacy of NSAIDs and acetaminophen. In orthopaedic surgery NSAIDs (including ibuprofen) and acetaminophen seem to be comparable, even though acetaminophen should be preferred because of its lower incidence of adverse effects. It may be appropriate to combine NSAIDs and paracetamol after major surgery, but more studies are required (102).

Ibuprofen and acetaminophen were assessed in comparison with placebo in a Cochrane systematic review of postoperative pain management. Ibuprofen 400 mg was shown to have a number needed to treat (NNT = the number of patients who need to be treated in order for one patient to achieve at least 50% pain relief) of 2.7 compared with placebo, whereas acetaminophen had an NNT of 4.6. The fact that the majority of the studies were dental studies constitutes a limitation of this systematic review (103). A more recent Cochrane review assessed the analgesic efficacy of ibuprofen in single oral doses for moderate and severe postoperative pain in adults. The very substantial amount of high quality evidence demonstrates that ibuprofen is an effective analgesic in treating postoperative pain. The NNTs for 200 mg and 400 mg ibuprofen were not significantly different. The authors concluded that NSAIDs are effective and are commonly prescribed to adult patients (104).

Chronic musculoskeletal diseases

Osteoarthritis

Osteoarthritis (OA), the most common form of arthritis, seems to be reaching epidemic proportions in western countries, a phenomenon clearly linked to increasing life

expectancy in this part of the world. For obvious economic reasons, therefore, these countries are engaged in the struggle to combat OA. According to the definition by the American College of Rheumatology, OA is a heterogeneous group of conditions that leads to joint signs and symptoms that are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone at the joint margins. The aetiology of OA is multifactorial and includes both generalised constitutional factors and local adverse mechanical factors, but further basic science investigations seem to be necessary since no definitive cure currently exists (105). The Rotterdam (106), Framingham (107), Fallon (108) and AMICA (109) studies have described the epidemiological features of OA.

Inflammatory cytokines and proteases contribute to the process of joint destruction (110) and exacerbation of nociception (111).

Individual differences in both the degree of inflammation and the susceptibility to nociception sensitisation may explain, at least in part, why some patients with limited disease imaging have severe pain, while other patients with more severe deterioration of the joint have minimal pain (112). For this reason, the use of analgesics without anti-inflammatory properties in the joints, such as acetaminophen/paracetamol, would provide only pain relief, without clinically beneficial anti-inflammatory activity (113,114).

At present, NSAIDs are commonly used to treat OA. Their analgesic and anti-inflammatory effects have been shown to be effective in improving pain and disability during OA (115-117).

Recently, the Osteoarthritis Research Society International (OARSI) recommended, for the management of OA of the knee and hip, the use of NSAIDs in symptomatic patients who have both pain and inflammation (118).

Ibuprofen appears to be the most frequently prescribed NSAID (119,120).

A recent study in India involving 1916 doctors from general or specialist practice showed ibuprofen to be the first choice NSAID with reportedly the best gastric tolerance (121).

Ibuprofen treatment, which is known to effectively reduce the signs and symptoms of OA, appeared to reduce cartilage and synovial tissue turnover as monitored by the urinary markers C-terminal crosslinking telopeptide of type II collagen (CTX-II) and urinary glucosyl galactosyl pyridinoline (Glc-Gal-PYD). Whether ibuprofen might also prevent cartilage loss and reduce synovium degradation in patients with OA remains to be investigated (17).

Many authors have tried to identify the dosage related to the best efficacy and tolerability of ibuprofen, but this issue remains controversial due to differences between the groups treated in the various attempts.

Recently the IPSO study concluded that ibuprofen 400mg as a single or multiple dose (1200 mg daily) is more effective than paracetamol 1000mg as a single or a multiple dose (3000mg daily) over a period of 14 days in patients affected by hip and knee OA (122).

Saag et al. showed that 2400 mg ibuprofen daily is effective in treating symptoms of pain and problems with mobility in OA as assessed by standardised clinical scores (123).

In a randomised, double-blind trial of 809 adults with knee and hip OA, Day et al. showed that ibuprofen at a dose of 800 mg thrice daily was clinically efficacious and safe during a six-week treatment period (124). Previously, Bradley et al. obtained similar results with 2400 mg daily but also with doses of 1200 mg daily in patients affected by knee OA (125).

In 1992, Di Peppe et al. reported a single-blind, randomised, parallel and balanced group study in which geriatric patients of both sexes affected by spondyloarthritis were treated with ibuprofen 1200 mg, two daily doses, versus naproxen 1000 mg, two daily doses, over a period of three weeks. The patients in the ibuprofen group showed a more rapid relief of pain (126).

In 1996, Earl et al. in a randomised, double-masked, double-dummy, parallel-group trial over a period of 4 weeks compared sustained release ibuprofen (1600 mg) with piroxicam (20 mg) once daily in elderly patients with osteoarthritis of the hip and/or knee. Ibuprofen was associated with a tendency towards better 24-hour control of pain and with lower gastric disturbances compared with piroxicam (127).

Hochberg et al., in 1995, found the dose of 1200 mg daily of ibuprofen to show greater efficacy over a short period than paracetamol in patients affected by knee OA (128).

Bliddal and coauthors, in a randomised study, evaluated the efficacy of ibuprofen on pain level and function in patients with OA of the hip or knee: ibuprofen 400 mg daily was found to be more effective than ginger extract and placebo during the three weeks of treatment, with no significant adverse events noted which could be ascribed to the active substances (129).

In a meta-analysis by Ashraf et al. (130) in elderly (>65 years) OA patients, the incidence of adverse events on ibuprofen 1200 mg daily was compared with that in patients receiving placebo. The study concluded that ibuprofen is safe in the elderly OA patient, a group who frequently self-administer the drug, confirming the findings of previous studies.

A Cochrane review examining the relative efficacy of different NSAIDs used in knee OA concluded that despite the large number of publications in this area, many trials were poorly designed, and there was no evidence to distinguish between the efficacy of equivalent recommended doses of conventional NSAIDs (131).

Recently, Reijman et al. hypothesised the existence of an association between NSAID use and progression of OA.In this large, population-based, prospective cohort study, the negative effect of NSAIDs on progression of hip and knee ROA was only found in the long-term use of diclofenac. However, the numbers seemed too low to allow the detection of an association between naproxen or piroxicam use and progression of OA (132).

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory autoimmune disorder. Although it preferentially targets the synovial lining of the joints, RA can also affect other organ systems including the lungs, heart, and blood vessels. The disease produces synovitis, secondary to hyperplasia of synovial cells and excess synovial fluid. The disease process often leads to the destruction of articular cartilage and ankylosis of the joints. Although the cause of RA is unknown, autoimmunity plays a pivotal role in both its chronicity and its progression.

Genetic polymorphisms of the major histocompatibility complex (MHC) II have been implicated in a predisposition to RA in various ethnic groups. MHC II encodes human leukocyte antigens (HLAs), and among those associated with an increased RA risk are HLA-DR1, HLA-DR4, HLA-DR6, and HLA-DR10 (133).
There is no known cure for RA, but many different types of treatment can alleviate symptoms and/or modify the disease process. Pharmacological treatments must be focused on alleviating the current symptoms, and on preventing the future destruction of the joints. Recently, guidelines and recommendations proposed by the American College of Rheumatology and the European League Against Rheumatism have included NSAIDs, glucocorticoids, disease-modifying anti-rheumatic drugs, and biological agents (134,135).
With growing understanding of the pathophysiology of RA, several drugs such as glucorticoids have lost their previous status as first-choice treatments; on the other hand, NSAIDs and other analgesics are still useful while the initial workup of the patient is being conducted and can continue to be used thereafter for the management of pain and inflammation (136).
The literature on indications and dosage of NSAIDs in RA appears very poor; Gotzsche found doubtful or invalid statements in 76% of the conclusions or abstracts of 196 clinical trials, 43 of which compared ibuprofen with other drugs; the author concluded "It is not obvious how a reliable meta-analysis could be done in these trials" (137).
Among NSAIDs, the selective COX 2 inhibitor as celecoxib showed a lower incidence of complications than traditional NSAIDs in the well known long-term CLASS safety study. The trial was reported as a three-arm trial comparing celecoxib 800 mg/day with ibuprofen 2400 mg/day and diclofenac (138).
In an editorial of 2002, Juni and coauthors presented their doubts and disappointed overoptimistic short term data about the CLASS study and its conclusions. They advocate an "industry independent," individual patient data meta–analysis of all large scale, long term trials of selective COX 2 inhibitors including both published and unpublished data (139). We agree with others authors, that on this field more and better designed studies are needed (140).
Historically, the efficacy of ibuprofen in RA was reported as long ago as 1968 in a double-blind crossover study from Scotland, which compared it with aspirin 5g/day and prednisolone 15mg/day (141).
In 1975, Godfrey and de la Cruz found a daily dosage of 2400 mg of ibuprofen to be more effective than 1200 mg daily during a 4-week double-blind trial in 41 patients with RA, but no intermediate drug dosage was studied (142).
In 1978, Pavelka et al. showed a therapeutic benefit with a dosage of up to 1600 mg daily over six months in 59 RA patients (143).
In 1983 Grennan et al. showed a significant response to 1600 mg daily of ibuprofen in RA patients, but increasing the daily dosage to 2400 mg produced no overall increase in response (144).
In 1984, Ward stated that 1200 mg/day or more of ibuprofen is as effective as aspirin and other NSAIDs in the treatment of RA (145). Moreover, in 1994, Fernandes et al. (146) reported that the once-daily dosage of 1600 mg ibuprofen in the sustained-release formulation is effective in the relief of symptoms associated with both OA and RA (Fig. 3).

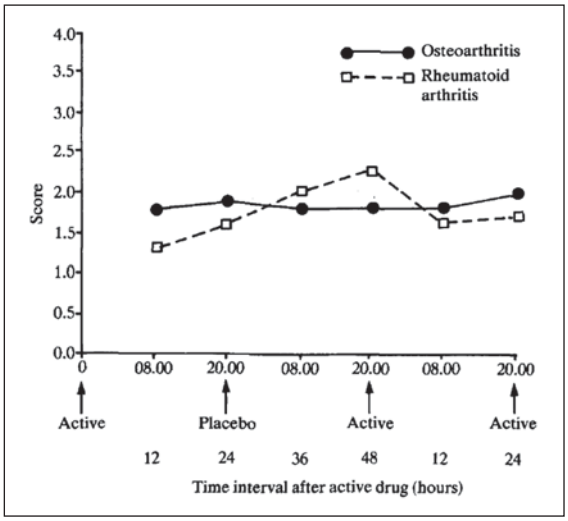

Figure 3 - Patients' assessment of pain and stiffness between the day after placebo and both the preceding and succeeding days: mean values of severity scores.

Effects of placebo administration on pain in patients with rheumatoid arthritis or with osteoarthritis treated for 13 days with 2x800 mg sustained-release ibuprofen tablets (ibuprofen) taken together every evening with the exception of a single day on which the active treatment was substituted by matching placebo tablets (placebo).

Juvenile rheumatoid arthritis
Juvenile rheumatoid arthritis (JRA) is the most common rheumatic condition in children, having a prevalence of approximately 30 to 150 per 100000. The course of JRA can be highly variable: some patients recover fully, whereas others experience lifelong symptoms and significant disability. The variability in the disease course may partly explain the misconception that JRA is usually a benign disease. However, an 80% remission rate by the time the child reaches adulthood has frequently been cited (147).
As with RA, the goals of therapy are to decrease chronic joint pain and suppress the inflammatory process; physicians dealing with paediatric patients, however, must also be concerned with their patients' need to achieve normal growth and development. Only a handful of NSAIDs have been approved by the FDA in the US for use in JRA (ibuprofen, naproxen, tolmetin, and choline magnesium trisalicylate) (148).
The dose of ibuprofen employed in juvenile arthritis (30-40 mg/kg/day) is much higher than that generally employed in infants and children for the treatment of fever and pain conditions (5-10 mg/kg/day). Among the earlier published reports of the pharmacokinetics of ibuprofen in JRA were two studies by Mäkela et al. (149,150).
In 1973, Ansell reported an open label investigation in eight patients (aged 7-14 years; 5 female, 3 male). Most were treated because they were unable to tolerate aspirin and had a prior history of dyspepsia or gastrointestinal bleeding or, in one case, because of poor control. Initially they received 200-300 mg/day (those with a body weight of 20-30 kg) or 400 mg (those weighing

over 30 kg). Later, all but one received 600 mg/day and one 1200 mg/day for apparently long periods of time (12-24 months). Satisfactory control of pain and stiffness were observed in six of eight cases, although in two of these the dose had to be increased before this was achieved. Occult blood which had been observed in the patients who were on aspirin became negative with ibuprofen (151).
Giannini et al., in 1990, reported a double-blind study in 92 children with JRA (mean age 7.7 years). Of these 45 received ibuprofen suspension 30 mg/kg/day and 47 aspirin 200 mg tablets or 300 mg caplets according to bodyweight (60 mg/kg/day) for 12 weeks. All the patients on ibuprofen showed reduction in all five measured joint parameters (morning stiffness, number of joints with swelling, number of joints with pain on motion, total number of the joints with active arthritis, overall severity score), while those that received aspirin showed significantly and clinically fewer reductions in joint inflammation and pain on motion, although the reduction in morning stiffness was the same in both groups (152).
Steans et al., in 1990, published a multicentre, open-label study with an average 8 months extension that examined the safety, efficacy and acceptability of 10 (initially) – 40 (maximum) mg/kg/day ibuprofen syrup in 46 children with JRA, mean age 6.8 years. Of the 39 children who completed the trial, 28 improved on therapy, seven became worse and four remained unchanged (153).
Pseudoporphyria may occur with all the propionic acid NSAIDs, but cases have also been reported with naproxen sodium, especially in fair-skinned young patients (154).
In summary, the literature, which only reports case series exploring the management of JRA with non-selective NSAIDs, shows no consensus on the best NSAID and best dosage to use.

Ankylosing spondylitis
Ankylosing spondylitis (AS) is a chronic, inflammatory, rheumatic disease characterised by inflammatory back pain due to sacroiliitis and spondylitis, peripheral arthritis, and the formation of syndesmophytes leading to ankylosis, which has long been a therapeutic challenge for clinicians. NSAIDs are well recognised as useful for symptom control and this efficacy is among the Amor classification diagnostic criteria for AS (155).
Recently, a prospective longitudinal study of 241 patients with AS examined the duration of treatment and discontinuations due to side effects of new courses of sulfasalazine, methotrexate, ibuprofen, naproxen, indomethacin, diclofenac, piroxicam, nabumetone, and celecoxib. Ibuprofen showed less side effects (6.7%) compared with the other drugs (156,157).
Recently the advent of tumour necrosis factor therapy has appeared to have an encouraging effect on the underlying disease process, but further studies are needed on AS patients (158).

Psoriatic arthritis
Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy presenting with a variable course, from mild synovitis to severe progressive erosive arthropathy, characterised by the association of arthritis and psoriasis. Its pathophysiology is still unclear. Furthermore, the mechanisms of action of the drugs currently employed to treat PsA are often incompletely documented. Generally mild arthritis can usually be controlled by NSAIDs, taken as required (159). Because NSAIDs can potentially shunt products of the inflammatory arachidonic acid cascade from the COX to the lipooxygenase pathway, concerns have been raised that the increased leukotriene load might provoke a flare up of skin lesions. Ibuprofen has not been investigated and only case series are present in the literature (160).

Haemophiliac arthropathy
Haemophiliac arthropathy is a common complication of severe and moderately affected factor-VIII- and factor-IX-deficient haemophiliacs. It usually involves a lengthy process consisting of pain, joint stiffness, decrease in range of motion, muscular atrophy, and a final stage of a nonfunctional joint. It is, without doubt, one of the major problems of haemophilia now that appropriate factor replacement is available to treat acute haemorrhage.
In the only reported double-blind individual crossover trial, the efficacy of 1600 mg daily during 16 weeks of ibuprofen administration to 20 haemophiliacs with haemophiliac arthropathy was demonstrated and no evidence of increased frequency or severity of haemophiliac bleeding episodes or clinical or laboratory evidence of bleeding was reported (161).

Primary fibromyalgia syndrome
Primary fibromyalgia syndrome (PFS) is a very poorly studied disease whose features are musculoskeletal pain, psychological distress, non-restorative sleep, fatigue, and specific regions of localised tenderness (trigger points), all in the absence of otherwise apparent organic disease. The aetiology of fibromyalgia is unclear, although accumulating data suggest that disordered central pain processing plays a role in its pathogenesis. The therapeutic effects of ibuprofen were evaluated in 46 patients affected by PFS in a double-blind, placebo-controlled study for three weeks and in an open trial for another three weeks. No significant differences were found between ibuprofen and placebo groups, but the authors observed that tender point sites among patients with fibromyalgia were more significant in the ibuprofen than in the placebo group ($p<0.001$) at three as well as six weeks (162).
In 1991, in a multidimensional evaluation, 78 patients with PFS were randomised to four groups for treatment with ibuprofen and/or alprazolam in a randomised, double-blind, double-dummy, placebo-controlled pilot trial. Clinical improvement in patient rating of disease severity and in the severity of tenderness upon palpation was most apparent in the subgroup of patients who were receiving both ibuprofen and alprazolam (163).
Recently in the United States a study was performed on 2596 patients selected with Internet access. The most commonly used medications were acetaminophen (ever used 94%), ibuprofen (ever used 87%), naproxen (ever used 66%), cyclobenzaprine (ever used 64%), and amitriptyline (ever used 55%). On the basis of percentages of respondents rating medications as helpful, the top 10 were: hydrocodone preparations (75%), aprazolam (70%), oxycodone preparations (67%), diazepam (65%), zolpidem (64%), clonazepam (61%), cyclobenzaprine (58%), codeine preparations (55%), propoxyphene preparations (54%), and ibuprofen (51%) (164).

From the literature on this topic, it appears very difficult to reach a scientific conclusion on the use of NSAIDs in patients affected by PFS. This is probably mainly because the aetiopathogenesis of this disease is still unknown. Further and better designed studies in the future should help to shed light on this area (165).

Heterotopic ossification

Heterotopic ossification (HO), also known as heterotopic bone formation (HBF), is the presence of bone in soft tissue where bone does not normally exist. Two forms have been described. The hereditary form is progressive myositis ossificans, while the acquired form is more common and is caused by trauma (such as fracture, fracture-dislocations, total hip arthroplasty (THA), hip osteotomy, or direct muscular trauma) or neurogenic causes (such as spinal cord injury or central nervous system injury) (166).

The use of NSAIDs has been advocated in the prevention of HO in patients submitted to THA, even though the aetiology remains unclear. It currently appears that primitive mesenchymal cells stimulated by surgical trauma proliferate, differentiate into osteoblastic cells, and produce osteoid matrix that is finally mineralised and transformed into bone tissue (167).

A recent Cochrane review concluded that perioperative NSAIDs appear to reduce the risk of HO by between a half and two-thirds. With routine use, such agents may be able to prevent 15-20 cases of HO in every 100 total hip replacements performed (168).

Persson et al., studying 144 patients submitted to THA, found less HO in these patients than in the placebo group after three and 12 months of follow up (169).

Recently Fransen et al. reported a randomised trial on 902 patients treated for 14 days with ibuprofen (1200 mg daily). Despite a decreased risk of ectopic bone formation (relative risk 0.69, 0.56 to 0.83), there emerged no significant differences as regards improvements in hip pain or physical function associated with ibuprofen (170).

All randomised clinical trials performed in this area are characterised by the lack of a placebo group; there is still no consensus on the best drugs, relative doses and duration of therapy. Further and better designed randomised trials are thus needed (171-173).

Adverse Drug Reactions

Gastrointestinal toxicity

The long-term use of classical NSAIDs is related to the development of adverse drug reactions (ADRs) such as gastric toxicity, which has precluded further extension of their therapeutic use (174).

In fact, prostaglandin E2 and prostacyclin are both hyperalgesic (elicit an increased sense of pain) and gastroprotective. Thus, non-selective COX inhibition with agents such as aspirin, ibuprofen, indomethacin, and naproxen, which inhibit both COX-1 and COX-2 enzymes, provides effective pain relief for inflammatory conditions but carries a risk of erosive gastritis and gastrointestinal bleeding. Selective COX-2 inhibitors (valdecoxib, rofecoxib, celecoxib, and others still under development) were developed to minimise gastrointestinal toxicity, because of the relative paucity of COX-2 expression in the gastrointestinal tract and the relative abundance of COX-2 expression in inflamed and painful tissues.

Previously we reported in a retrospective study that NSAIDs caused >55% of the ADRs detected in hospitalised patients and that these are common in patients aged >61 years. Moreover, we reported that the ADRs induced by NSAIDs affected skin, the gastrointestinal and respiratory systems and that the drugs more commonly involved were diclofenac and aspirin (175).

A systemic review of studies that examined the relative risks of gastrointestinal complications associated with different NSAIDs found ibuprofen to be the least toxic NSAID (176). Lugardon and coworkers reported that patients treated with ibuprofen had a low risk of gastrointestinal events compared with those treated with diclofenac, naproxen, ketoprofen, celecoxib, piroxicam (177). Moreover, Moore described that during NSAID treatment, significant gastrointestinal adverse effects were more common with aspirin (7.1%) and acetaminophen (5.3%) than with ibuprofen (4%) (178). The lowest rates of occurrence of gastrointestinal complications in patients treated with ibuprofen could be attributed to its short half-life (about 2 hours). Thus, there is good pharmacokinetic rationale to account for the low rate of gastrointestinal ADRs with ibuprofen.

As regards the prevention of NSAID-induced upper gastrointestinal toxicity, a 2002 Cochrane review included 40 randomised controlled trials and concluded that all doses of misoprostol significantly reduced the risk of endoscopic ulcers. Standard doses of histamine-2 receptor antagonists effectively reduced the risk of endoscopic duodenal but not gastric ulcers. Double doses of histamine-2 receptor antagonists and protein pump inhibitors effectively reduced the risk of endoscopic duodenal and gastric ulcers, and were better tolerated than misoprostol (179).

In 1996, Henry and coauthors (176) identified 12 controlled epidemiological studies examining 14 drugs for which safety data relative to ibuprofen could be derived. The data supported the conclusion of the Committee on Safety in Medicines that ibuprofen is the lowest risk NSAID and azapropazone the highest risk agent. The review also presented evidence that the risk of gastrointestinal injury from NSAIDs is greater at higher doses.

Liver toxicity

Several papers have described fatal hepatotoxicity in patients receiving both conventional NSAIDs and coxibs e.g. diclofenac, nimesulide, celecoxib, lumiracoxib (180-182) as well as acetaminophen (183).

Moreover, we also reported that nimesulide is able to induce liver toxicity probably through the hepatic bioactivation of nimesulide; indeed, hepatic bioactivation of nimesulide produces reactive metabolites that have the potential to induce intracellular oxidative stress and mitochondrial injury (184). Acetaminophen use could be related to a dose-dependent development of liver toxicity (185), therefore the dose/day should be lower than 4g, as indicated by the FDA (186).

Indeed, at higher doses acetaminophen is metabolised by CYP2E1 into a toxic metabolite (N-acetyl-p-benzoquinoneimine) (187) that, reducing the detoxification

system of glutathione, can induce the death of hepatocytes.
By contrast, hepatic reactions are probably rarely associated with ibuprofen. Since there have been no specific indications of reports of hepatic reactions with OTC use of ibuprofen from trials (122,188) or in literature analyses (189) it is likely that hepatotoxicity is not a significant risk factor at OTC dosages.
Accordingly, Italian data (190) documented that the percentage of patients with liver toxicity during NSAID treatment was very low during ibuprofen treatment (1.4) with respect to other NSAIDs (diclofenac 2.8; ketorolac: 4.6; nimesulide 13.8).

Cardiovascular safety

NSAIDs and coxibs are likely to induce serious cardiovascular events. In the cardiovascular system, prostacyclin derived from the metabolism of arachidonic acid is the dominant prostanoid produced by endothelial cells and is able to regulate complex interactions between platelets and the vessel wall, antagonising aggregation through the binding with platelet IPF receptors (191,192). Platelets contain only COX-1, which converts arachidonic acid to the potent proaggregatory, vasoconstrictive eicosanoid thromboxane A2 (TXA2), the major COX product formed by platelets. Non-selective COX inhibition with aspirin is effective for arterial thrombosis because of its ability to reduce COX-1-dependent production of platelet TXA2; by contrast, selective inhibition of COX-2 (rofecoxib and celecoxib) could produce a relative reduction in endothelial production of prostacyclin, while leaving the platelet production of TXA2 intact, increasing the risk of thrombotic cardiovascular events (193).
In particular, CV events, including myocardial infarction and hypertension, were noted particularly with rofecoxib (194).
Chou et al., reported that serious coronary heart disease incidence rate ratios were much higher for rofecoxib (RR, 2.29; 95% CI, 1.24-4.22; p=0.008) at a more than 25 mg dose with respect to celecoxib (RR, 1.61; 95% CI, 1.01-2.57; p=0.046) at a more than 200 mg dose (195). However, celecoxib is also able to significantly increase the risk of cardiovascular events in a dose-dependent manner (196).
COX-2 inhibitors may increase CV risk at high doses through the activation of thrombosis via decreased PGI2 production in the endothelium and unchecked production of TXA2 by COX-1. The imbalance in circulating levels of PGI2 and TXA2 results in increased vascular tone, platelet aggregation, and vascular smooth muscle proliferation due to the unopposed TXA2 effects (197).
No conclusive data concerning CV safety were reported during acetaminophen treatment. Indeed, Curhan et al. (198) and Chan et al. (199) reported an increase in CV events in women treated with acetaminophen; however, this increase was the same as that associated with common NSAIDs (RR1.35 and RR 1.44, respectively).
By contrast, ibuprofen seems to show a low risk of CV events. Rahme and Nedjar (200) showed the following adjusted hazard ratios: ibuprofen 1.05 (0.74-2.41), diclofenac 1.69 (1.35-2.10), naproxen 1.59 (1.31-1.93), celecoxib 1.34 (1.19-1.52), rofecoxib 1.27 (1.13-1.42), and acetaminophen 1.29 (1.17-1.42).

In agreement with these data, recently, at the 2010 congress of the European Society of Cardiology (ESC), it was reported that in people living in Denmark, NSAID use was associated with an increased risk of stroke ranging from about 30% with ibuprofen and naproxen to 86% with diclofenac (see Table IV).

Table IV - Risk of stroke with several NSAIDs

NSAID	HR (95% CI) for risk of stroke
Ibuprofen	1.28 (1.14-1.44)
Diclofenac	1.86 (1.58-2.19)
Rofecoxib	1.61 (1.14-2.29)
Celecoxib	1.69 (1.11-2.26)
Naproxen	1.35 (1.01-1.79)

NSAIDs and bone

COX1 is expressed in normal bone, while COX2 is upregulated during bone repair and in the presence of several stimuli such as inflammation. In particular, has been reported that PGE2 is able to induce resorption during inflammatory diseases (201).
However, no definitive data have been reported in experimental models regarding the effects of conventional non-selective NSAIDs (ibuprofen, naproxen and ketorolac) on long bone fracture healing. In fact while Radi et al. (202) reported inhibitory effects on long bone fracture healing, other authors failed to document it (203).
As with conventional NSAIDS, there are also controversies related to coxib (204,205).

NSAIDs and drug interactions

Displacement to plasma proteins

Free NSAID concentrations (i.e. those non-bound to albumin) are generally regarded as pharmacologically relevant to the actions of these drugs, as well as to the untoward effects of drug-drug interactions, where the toxic effects of NSAIDs or other drugs are due to displacement of one or other from the albumin or other plasma proteins. As with many NSAIDs, most of which bind strongly to plasma proteins (around 99%), ibuprofen also binds strongly to albumin (206). In particular as reported in Table V, ibuprofen binds to site II (benzodiazepine) of albumin, while salicylates, diclofenac and naproxen bind to site I.
Therefore, diclofenac is more likely to show a drug-drug interaction with warfarin than ibuprofen. This is in agreement with recent guidelines suggesting a treatment with ibuprofen in patient chronically treated with warfarin.

Liver metabolism

Inhibition of CYP-2C8 by administration of gemfibrozil to humans increases the plasma concentrations of

Table V - Drugs binding to site I (warfarin) or II (benzodiazepines) of albumin

Site I (warfarin)	Site II (benzodiazepines)
Chlorothiazide	Ketoprofen
Phenytoin	Ibuprofen
Glibenclamide	Indomethacin
Naproxen	Dicloxacilline
Salicylates	Nimesulide
Nimesulide	
Diclofenac	
Sulphamidics	
Fluoroquinolones	
Valproate	

R(-)-ibuprofen by about one third as well as prolonging the elimination half lives of R(-) and S(+) by 54% and 34%, respectively, and increasing AUC values by about 20% (207), suggesting that CYP-2C8 plays a major role in oxidative metabolism of the ibuprofen enantiomers.
However, at present there are no data on the inhibitory effects of ibuprofen on CYP enzymes. Conversely, it has been well documented that celecoxib is an important inhibitor of CYP2D6 and increases the area under the serum concentration-time curve of metoprolol (about 64%) (208).

Renal excretion

Several reports suggest that NSAIDs are able to inhibit the renal excretion of digoxin, lithium and tacrolimus (33,209,210).
Moreover, Igbal and coworkers documented that diclofenac induces an increase in the plasma AUC of ciprofloxacin, but reduces total body clearance (211).
As documented by Karjalainen et al. (212), diclofenac is not a CYP inhibitor, but it induces a dose-dependent inhibition of OAT-1-4 pumps involved in renal excretion (213). With this mechanism, authors documented that diclofenac is able to increase the rosuvastatin plasma concentration (214). Moreover, diclofenac and salicylates are also able to increase the plasma concentration of metothrexate through the competition with the excretion via on MRP 2 and 4 renal pumps.

Aspirin-NSAID interactions

Previously, Catella-Lawson et al. (215) documented in healthy patients that ibuprofen may interfere with the antiplatelet effects of aspirin. In fact, the authors treated healthy patients with aspirin (81 mg) taken 2 h before ibuprofen (400 mg) each morning for six days and then evaluated the synthesis of prostaglandins. The authors documented that when aspirin was given either before or after ibuprofen, there was complete inhibition of the effect of aspirin on serum thromboxane and platelet aggregation. This impairment of platelet aggregation and thromboxane production by ibuprofen was not evident with paracetamol, diclofenac or rofecoxib. By contrast, Kimmel et al. (216) reported that in patients with no history of coronary artery disease the use of aspirin was associated with a lower risk of myocardial infarction, as expected, but this benefit was not seen in patients who took any NSAID in addition to aspirin. Patients with established coronary disease, who used aspirin with NSAIDs had a similar risk of developing myocardial infarction to that of patients who had taken aspirin alone. Moreover, in elderly patients with a history of myocardial infarction the mortality of those who had received aspirin and a non-steroidal drug was similar to that of patients who had been prescribed aspirin alone (217,218). No apparent differences were observed in the mortality and analysis of patients who had been prescribed aspirin and ibuprofen compared with those prescribed aspirin alone (217). Moreover, Cryer et al., showed that prior treatment for 8 days with aspirin is not affected by subsequent ibuprofen treatment in terms of platelet thromboxane production (219).
By contrast, Schujit et al. (220) recently reported in healthy volunteers more thrombotic cardiovascular events (2.14%) during ibuprofen/aspirin therapy than patients using lumiracoxib combined with aspirin (0.25%; $p < 0.03$), even though no difference was observed in a subgroup using ibuprofen or lumiracoxib alone (0.92% vs 0.80% respectively). Therefore, these authors suggest that diclofenac should be preferred to ibuprofen for combined use with aspirin. Conversely in 2007, the FDA stated on its MedWatch website (221) that with concomitant use of ibuprofen and aspirin there is likely to be a minimal risk from any attenuation of the anti-platelet effects of low-dose aspirin because of the long-lasting effect of aspirin on platelets. Moreover, they state that patients who use immediate release aspirin (not enteric-coated) and take a single dose of ibuprofen 400 mg should take the dose of ibuprofen at least 30 min or longer after the aspirin to avoid attenuation of the effect of aspirin on platelets. Therefore, on the basis of FDA information and the available published literature it is clear that separation of the dose of aspirin from that of ibuprofen is a practical means of avoiding the potential for impairment of the anti-platelet effect of aspirin by ibuprofen. It should be noted that an earlier study in patients with rheumatoid arthritis (222) showed that with high-dose aspirin (3.6 g day-1), but not a lower dose of 2.4 g day-1, in combination with high- or low-dose ibuprofen there was a weak clinical additive effect on indices of articular function and pain and this appeared to be related to an increase in serum ibuprofen by aspirin, but ibuprofen administration did not affect serum salicylate levels. Thus, high doses of aspirin (not those usually used for anti-thrombotic effects) may have some impact on the clinical efficacy of ibuprofen in a positive sense, but this is related to effects on ibuprofen concentration in the plasma.

NSAIDs-antihypertensive drugs

A negative interaction between NSAIDs and antihypertensive therapy has previously been reported. However,

in a study in stage 1 and 2 hypertensive patients on low and high sodium diets receiving the angiotensin-converting enzyme (ACE) inhibitor, enalapril, ibuprofen 1200 mg day-1 did not affect systolic or diastolic blood pressure, although in a related study indomethacin reduced the effects of capropril (223). Other NSAIDs are well-known to interfere with the actions of ACE inhibitors (224). Conversely, inhibition of the renin-angiotensin system upregulates COX-2 (225) and thus may exacerbate the renal effects of NSAIDs. Calcium channel blockers do not appear to be affected by ibuprofen and other NSAIDs in hypertensive patients (226).

Concluding remarks

In conclusion, the literature data document that NSAIDs are the most widely used drugs for pain management in musculoskeletal disorders and their effects seem to have been well evaluated as regards both side effects and drug interactions. Therefore, weighing up both clinical efficacy and side effects, ibuprofen emerges as a good choice both for children and adults, and especially for patients on polytherapy regimens or under treatment with oral anticoagulant agents or aspirin-like agents.

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