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Review

Osteoarthritis of the knee and hip. Part II: therapy with ibuprofen and a review of clinical trials

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Abstract

Objectives We review the pharmacological properties and clinical evidence pertaining to the efficacy of ibuprofen as a first-line treatment in hip and knee osteoarthritis (OA). In the context of our previous paper's exploration of the aetiology and pathogenesis of OA as a basis for pharmacotherapy, we discuss the pharmacokinetics (PK) and clinical pharmacodynamics (PD) of ibuprofen relevant to OA.

Key findings Although widely used, the benefits and risks of ibuprofen, especially compared with other non-steroidal anti-inflammatory drugs (NSAIDs) and placebo, have only recently been evaluated in OA of the hip and knee in randomized-controlled clinical trials (RCT). The efficacy and occurrence of adverse reactions from ibuprofen was compared with placebo in a structural review of the literature and systematic review of RCTs in large-scale clinical trials. Ibuprofen has been found to result in approximately 50–60% improvement over placebo in WOMAC scores, including those reflecting inflammatory joint pain in knee and hip OA or other indices of pain, disability and impaired function. Mega-trials performed in comparison with the newer NSAIDs, the coxibs, have shown that ibuprofen has comparable therapeutic benefits and although serious gastrointestinal conditions are sometimes more frequent after short-term treatment, longer-term (several months) therapy in OA reduces the advantages of the coxibs over other NSAIDs including ibuprofen. Cardiovascular risk, though present with coxibs and some NSAIDs in OA, is lower or slightly so with ibuprofen compared with coxibs.

Summary Ibuprofen is effective and relatively safe (especially at low over-the-counter doses and in the short term) for mild-to-moderate OA of the knee and hip. The PK properties of ibuprofen in OA (short plasma $t^1/_2$) confer advantages of this drug for OA, while evidence for clinically relevant PD benefits in joints of patients with OA, though limited, is suggestive of local anti-inflammatory activity.

Introduction

Ibuprofen has a broad range of applications in the clinical setting and is one of the most commonly used antipyretic, anti-inflammatory and analgesic drugs. In addition to its use specifically in treating rheumatic disorders, such as osteoarthritis (OA), the aforementioned properties lend it well to the treatment of general symptoms of acute pain, fever and inflammation. This paper outlines the pharmacology and clinical aspects of the use of ibuprofen in OA, with special reference to OA of knees and hips. This culminates in a systematic analysis of randomized placebo-controlled trials or reference drug-controlled trials of ibuprofen, where we consider the merits and limitations of its use as a first-line treatment of knee or hip OA. Ibuprofen is a member of the class of drugs known as 2-arylpropionic acid derivatives, also referred to as the 'profens' or chemically as propionic acids.

The 2-arylpropionic acids have been in use for over forty years and fall within the category of non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are a heterogeneous group of agents with overlapping and sometimes redundant therapeutic effects and mechanisms. The continual development of the NSAID group with numerous pharmacological agents is probably reflective of the still unsatisfied need for effective management of pain in musculoskeletal conditions along with significant variability in response to these drugs between individuals.[1,2] Members of the propionic acid group, along with ibuprofen, include naproxen, ketoprofen

Table 1 Adapted from Evans (1996)[1]

List of compounds belonging to the profen (2-aryl propionic acid) class		
Alminoprofen	Flurbiprofen	Pirprofen
Benoxaprofen	Ibuprofen	Pranoprofen
Bermoprofen	Indoprofen	Suprofen
Carprofen	Ketoprofen	Tiaprofenic acid
Cicloprofen	Loxoprofen	Ximoprofen
Fenoprofen	Microprofen	Oxaprozin
Flunoxaprofen	Naproxen	

and flurbiprofen; these share many biochemical properties and clinical effects but vary in many regards including potencies and toxicity profiles (Table 1). Ibuprofen is often the first-choice drug among the propionic acids due to its relatively low risk of adverse effects.[1,3]

The chemical formula of ibuprofen is $C_{13}H_{18}O_2$ and its chemical name, given by IUPAC standard nomenclature, is 2-(4-isobutylphenyl) propionic acid.[4] Profens are weak acids by nature due to the presence of a carboxylic acid functional group.[1] Most of the propionic acids have a characteristic chiral centre at C-2 next to the carboxylic group, giving rise to the existence of enantiomeric pairs. Enantiomerism is a type of stereoisomerism; more specifically, enantiomers are two molecules that share the same chemical formula and are mirror images of each other but are not superimposable. Given the fact that the behaviour of enantiomers may differ from each other when interacting with chiral substrates of the body, stereospecificity is thus a pertinent factor to consider in the analysis of ibuprofen's pharmacokinetics and pharmacodynamics.[3]

The history of ibuprofen itself is intertwined with an enhancement of our understanding of inflammatory mechanisms in rheumatic diseases and how they may be therapeutically modified. Although aspirin, a prominent NSAID, has been in wide use since the early 1900s, the mechanisms of action were not adequately explored until the advent of ibuprofen.[5,6] The development of ibuprofen, along with many other propionic acid agents, stemmed from the search for a non-corticosteroid drug to treat rheumatic diseases while maintaining reasonable gastrointestinal tolerability.[5,6] The endeavour was initiated by Stewart Adams and colleagues of Boots Pure Drug Company in the mid 1950s, and was driven in part by Adams' conviction that the analgesic effects of aspirin result not only from central mechanisms but also from anti-inflammatory effects.[5,6] His vision was to develop a drug more potent than aspirin, safer than phenylbutazone and devoid of the undesirable hormonal interferences caused by corticosteroids (the available rheumatic treatment options at the time). Working with organic chemist John Nicholson, the team synthesized a multitude of potential agents and were largely guided by the use of a modified guinea-pig UV erythema assay as a model of assessing their anti-inflammatory activity. The Randall–Sellito assay was later introduced and employed in concert with the erythema assay as a means of assessing analgesic activity. The ideal anti-rheumatic drug should possess the triad of analgesic, antipyretic and anti-inflammatory activity. Ibuprofen was not the most potent agent by these standards but, of the preferred candidates, it appeared to potentially have the best safety profile.[5,6]

Ibuprofen first entered the UK market in 1969 as a prescription medication and then the US market in the 1970s. It was indicated for use in the treatment of painful conditions, particularly those of musculoskeletal origin such as rheumatic diseases. Ibuprofen was initially used cautiously by clinicians, at low doses of 400–1200 mg/day, and increased to the current maximum adult dosage of 2400 mg/day as confidence in its safety grew.[5] While other NSAIDs have been withdrawn due to toxicity, ibuprofen has maintained its high level of usage and reputation as one of the safest NSAIDs with fewest adverse effects.[7,8] Ibuprofen was approved for over-the-counter (OTC) non-prescription use in the UK in 1983, where it was first marketed as Nurofen. OTC status followed in the USA, under the brand Advil.[3] Currently, ibuprofen trails only aspirin and paracetamol (acetaminophen) in terms of non-prescription OTC usage for managing pain, inflammation and fever. Of these, OTC ibuprofen is least toxic. Paracetamol is a significant competitor with ibuprofen, both in the OTC field and in the higher dose prescription range for treating rheumatic diseases like OA. Given their seemingly disparate paths of action, there is a possibility their effects can be synergistic or additive. Attention has been drawn to the greater risk of gastrointestinal and renal adverse effects with ibuprofen compared with paracetamol, but this is negligible in the OTC dose range. At the higher doses used in rheumatic therapy, this increased risk with ibuprofen is 'marginal'. However, ibuprofen does not share paracetamol's troubling hepatotoxic profile.[9] The inclusion of ibuprofen in the WHO's list of essential medicines is a testament to its place in modern healthcare.[10] Ibuprofen naturally has a strong odour and bitter taste, creating a burning sensation in the throat. Most commonly taken in solid oral form, this can be masked by coating tablets or capsules with alternative flavours.[11]

Ibuprofen pharmacokinetics and pharmacodynamics

Chiral inversion

Both in prescription and OTC forms, ibuprofen is conventionally administered orally as a racemate, meaning it exists as an equal mixture of the *S*-(+) enantiomer and the *R*-(−) enantiomer (Figure 1). Only the *S* enantiomer is active in inhibiting prostaglandin synthesis, which is now understood to be the primary anti-inflammatory mechanism of NSAIDs. The pharmacodynamics will be discussed subsequently. As is

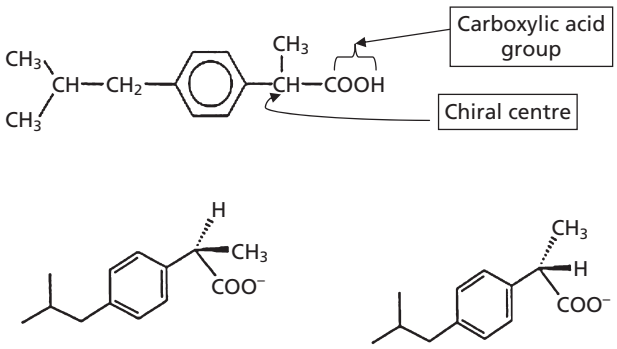

Figure 1 *R*-(–)-ibuprofen and *S*-(+)-ibuprofen. Note the difference in the 3D spatial arrangement of constituents on C-2, the chiral centre.

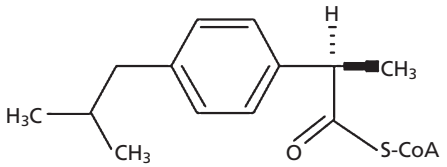

Figure 2 *R*-ibuprofen-CoA thioester (intermediate).

common amongst the 2-aryl propionic acid derivatives, ibuprofen undergoes metabolic chiral inversion upon administration. There is a unidirectional conversion of about 40–60% of *R*-ibuprofen into *S*-ibuprofen.[3,9] This inversion occurs pre-systemically (intestinal epithelium) and systemically (liver). The liver is the major site of systemic inversion and originally it was thought that inversion only occurs systemically. However, evidence for a pre-systemic component is apparent, given the fact that oral formulations with longer absorption times show greater chiral inversion corresponding to a greater time of contact with the intestine. This is supportive of the role of intestinal pre-systemic inversion. Also, Jamali *et al*.[12] noted significant chiral inversion of ibuprofen when it was incubated in excised intestinal segments. Notably, in formulations that are absorbed rapidly, the contribution of pre-systemic inversion is minimized.[3]

For the change in configuration (referred to as epimerization) to occur, ultimately the C-2 adjacent to the carboxyl group must become planar, a process involving beta oxidation where a proton is extracted and a carbanion is formed at C-2. The first step is formation of an *R*-ibuprofen-CoA ester, a prerequisite intermediate in the process (Figure 2). This is facilitated by liver long-chain acyl CoA synthetase (LCACS), which catalyses the reaction of ATP with ibuprofen to give ibupropyl pentanoic-AMP. LCACS further catalyses thioesterification, with AMP as a leaving group, to give the *R*-ibuprofen-CoA intermediate. Note that this first step is stereoselective for the *R* enantiomer, explaining why *S*-ibuprofen does not undergo inversion.

The acidity of the hydrogen (proton) on C-2 is increased by the presence of a thioester bond. However, the pKa of this H^+ proton is still greater than 10 and is thus not able to dissociate without the catalysis provided by epimerase. This enzyme is thought to link the hydrogen atom to a base residue on the enzymatic active site, thereby facilitating extraction of the H^+ proton and giving rise to a carbanion. Due to the carbanion's instability, tautomerism occurs and a double bond forms between C-1 and C-2. With the planar formation now achieved, H^+ protons can attack C-2 in an electrophilic addition reaction resulting in *S*-ibuprofen-CoA. Finally, with chiral inversion of the stereocentre complete, *S*-ibuprofen Co-A is hydrolysed to become *S*-ibuprofen by the acyl-CoA thioesterase enzyme. The metabolism of fatty acids can be seen as a model for ibuprofen's metabolic chiral inversion, given that both processes involve CoA esters and that ibuprofen bears structural similarity to fatty acids.[3,9]

Absorption and plasma kinetics

As is the case with most propionic acids, ibuprofen is absorbed well by the upper gastrointestinal tract.[1] Peak concentrations of ibuprofen occur in the plasma about 1–2 h after oral administration. It must be noted, however, that absorption rates may vary depending on whether a sustained-release or immediate-release formulation is administered. Given the slower absorption rate of sustained-release formulations, a higher ratio of *S* : *R* ibuprofen enantiomers is found in the plasma than occurs normally, presumably since this formulation has more time to undergo presystemic inversion in the intestinal environment. The Liquigel or other liquid formulations have the fastest absorption and are ideal for scenarios where rapid analgesic effects are desired.[9] Absorption of ibuprofen is not thought to be enantioselective, as the propionic acids are absorbed through a passive mechanism facilitated by the proton gradient in the gastrointestinal tract.[3] However, the possibility of active transport via a monocarboxylic transporter, which may lend an element of enantioselectivity to the absorption process, cannot fully be excluded.[3] Even if one were to assume that absorption is non-enantioselective, it is important to note that the absorption properties of a pure enantiomer differ from a racemic formulation, due to different physico-chemical properties between the two formulations (possibly because of inter-enantiomer interactions affecting dissolution). This gives rise to different kinetics for a racemate relative to either enantiomer administered alone.[1,13] In most cases of oral administration, there is almost complete bioavailability of the drug systemically, regardless of variation in absorption rates.[13] In one study, ibuprofen was administered orally and intravenously in identical doses. Results based on area under the plasma concentration–time curve (AUC) showed that the absolute bioavailability of the oral dose was usually over 92%

of the total intravenous dose available.[9] It is generally recommended that food be taken with ibuprofen to reduce the risk of upper gastrointestinal adverse events. Supporting the beneficial nature of this recommendation is the fact that concomitant food intake does not noticeably affect the rate or extent of ibuprofen absorption.[13]

The half-life (t½) of ibuprofen is about 2 h, which is relatively short compared with other propionic acids and NSAIDs in general. In contrast to ibuprofen, NSAIDs such as naproxen, with longer half-lives, exhibit greater variability between subjects in terms of accumulation and long-term steady-state plasma concentrations.[1] The short ½ of ibuprofen is thought to be a contributing factor towards its relatively low toxicity and incidence of adverse events. Ibuprofen, has fairly consistent properties; measures such as plasma concentration and AUC show clear dose relationships and kinetic constants such as t½ show little inter-patient or intra-patient variability.[9]

In the plasma, ibuprofen is extensively bound to proteins, the most common one being albumin. At therapeutic drug levels, over 99% of both ibuprofen enantiomers are protein bound. Because of this extensive binding, ibuprofen has a low volume of distribution, usually in the range of 10–20 l in humans.[13] Albumin exhibits enantioselectivity in the binding of ibuprofen, with 0.6% of *S*-ibuprofen unbound compared with 0.4% of *R*-ibuprofen unbound in plasma.[1] Additionally, the mean unbound ratio of *S* : *R* based on the AUC has been found to be 2.2, which is greater than the total (bound + unbound) ratio of *S* : *R*, at 1.4.[13] Both enantiomers share a common high-affinity binding site (a diazepam binding site) on albumin, whose binding constant for *R*-ibuprofen is 2.6 times greater than for *S*-ibuprofen. This lower extent of *S*-ibuprofen binding to albumin may contribute to its higher transfer rate into synovial fluid, where it ultimately exerts its effects.[3] It is generally the unbound portion of the drug that is considered pharmacologically active.

Given that the synovium is the presumed main site of action of NSAIDs, an understanding of ibuprofen's kinetics in the synovial fluid is important. Ibuprofen tends to accumulate in the synovial fluid, with broad peaks over 2–6 h, thus persisting in synovial fluid well past the plasma peaks.[9] A study by Day *et al*.[14] quantitatively examined the kinetics of ibuprofen in synovial fluid of arthritis patients. Tmax, the time for maximal concentration to be reached after administration of a dose, was found to be longer in synovial fluid than in plasma for both *R* and *S* enantiomers. The authors noted a delayed and extended period of time over which uptake into the synovial fluid occurs. This characteristic helps explain why even though the plasma concentrations decline rapidly (t½ of 2 h), ibuprofen is still effective when administered every 12 h.[13] The extent of ibuprofen binding to carrier proteins is less in synovial fluid than in plasma, which is congruent with a lower concentration of albumin in synovial fluid.[13,14,15]

Metabolism and clearance

Drugs belonging to the propionic acid class are excreted in the urine, primarily as metabolic products. Metabolism of ibuprofen occurs in the liver, and excretion of the parent drug along with metabolites is achieved mainly by the kidneys.[6] Excretion in the bile is a minor route and accounts for only about 1% of the dose,[16] whereas most of ibuprofen and its metabolites are accounted for in urine within a period of 24 h after administration. The percentage of ingested drug recovered in urine as intact ibuprofen and metabolites has been reported as 50%[9,16] and also as 60–70% in different studies.[17] The metabolism of ibuprofen is an oxidative process that involves enzymes of the cytochrome p450 family (CYP-450). When racemic ibuprofen is administered, a set of metabolites is formed for each enantiomer.[1] In phase I metabolism, the isobutyl chain of ibuprofen is hydroxylated to give 2-hydroxyl or 3-hydroxyl metabolites. These can be further oxidized to carboxyl metabolites such as 3-carboxy ibuprofen and 2-carboxy propionate. This whole process is catalysed by CYP-2C9 and CYP-2C8, two CYP-450 isoforms which differ in involvement depending on the enantiomer being metabolized.[9] CYP-2C9 has *S*-(+) hydroxylase activity, meaning that it preferentially oxidizes *S*-(+) ibuprofen to form *S*-(+)-2 and *S*-(+)-3 hydroxyibuprofen metabolites. On the other hand, CYP-2C8 preferentially oxidizes *R*-(−)-ibuprofen to give *R*-(−)-2 hydroxyibuprofen metabolites.[18]

Both the parent drug and the phase I hydroxyl and carboxyl metabolites can undergo conjugation with glucuronic acid to yield acyl and phenolic glucuronides, referred to as phase II metabolites.[1,9] There are 15 types of UDP-glucuronyltransferases that catalyse the formation of glucuronides in the liver. Because these enzymes only begin to develop between birth and six months of age, children have a comparatively low ability to detoxify the drug through glucuronidation.[9]

As stated above, these phase II metabolites are largely excreted by the kidneys and are thus found in urine. With regard to the *R* enantiomer of ibuprofen in particular, there is also the possibility of forming another type of metabolite, that being the stereoselective formation of ibuprofen-CoA thioesters (described above as being a process exclusive to the *R* enantiomer). The ibuprofen-CoA thioester is grouped in lipid stores as hybrid triglycerides that incorporate ibuprofen. These stores can then take part in general pathways of lipid metabolism.[1]

Modes of action

As mentioned previously, ibuprofen is involved in controlling pain, acute inflammation and fever. It does so by acting on various pathways and cellular signalling systems involved in inflammation – much of this milieu of interactions is not entirely clear at this time.[9] The main pharmacodynamic

actions involved in achieving this effect, centre around the reduction in prostaglandin production. Prostaglandins are inflammatory mediators that contribute to pain and inflammation, and are derived from arachidonic acid in a process mediated by the cyclooxygenase enzymes, COX-1 and COX-2. Thus, ibuprofen can be seen to inhibit this COX-mediated production of prostaglandins.[1] Different NSAIDs inhibit COX-1 and COX-2 with varying degrees of selectivity. Prostaglandin E_2 (PGE_2) is the main mediator of pyresis and is produced in the hypothalamus. COX-2 is the inducible enzyme active in amplifying the production of PGE_2 during inflammation. *S*-(+)-ibuprofen (the active enantiomer) targets COX-2 and inhibits this synthetic process in the peripheral and central nervous system, thereby reducing PGE_2 levels and providing the primary source of pain relief.[9] The plasma profile of *S*-ibuprofen demonstrates parallel consistency with analgesic effects and prostaglandin inhibition. In a double-blind placebo-controlled crossover randomized-controlled clinical trial (RCT), Suri and coworkers demonstrated, with the use of somatosensory evoked potentials (SEP) and subjective pain relief data, that the peak analgesic effects of ibuprofen occur around 2.5 h after administration.[19] With regard to plasma levels, peak values occur at 1.3 and 2.2 h for *R*-ibuprofen and *S*-ibuprofen, respectively, supporting the claim that the *S* enantiomer is in fact the predominant driver of the analgesic effect.[9]

Ibuprofen and the other NSAIDs also inhibit COX-1, a constitutive enzyme that produces many prostaglandins mainly with 'housekeeping' functions. In fact, some prostaglandins are important protectants in the gastrointestinal tract and also play a role in regulating renal perfusion. The concomitant inhibition of COX-1 by *S*-ibuprofen is thought to underlie some of the adverse effects associated with ibuprofen, such as gastric ulcers, gastrointestinal bleeding and renal dysfunction.[9] Understandably then, it is hypothesized that the ratio of COX-1 versus COX-2 inhibition by a given NSAID bears relation to the toxicity of the drug. That is, if a drug favours COX-1 inhibition, it may be suspected to exhibit higher toxicity. This concept underlay the development of COX-2 selective inhibitors, known as coxibs (e.g. celecoxib, rofecoxib), in the late 1990s, which appeared to successfully reduce gastrointestinal and renal adverse events.[9] However, a number of coxibs were subsequently withdrawn due to the occurrence of cardiovascular adverse events. Ibuprofen has one of the lowest gastrointestinal and renal toxicity profiles of all the traditional NSAIDs, but this cannot be predicted by looking solely at its COX-1/COX-2 selectivity (not necessarily correlated to toxicity).[20] A factor likely contributing to its relatively low incidence of adverse effects is the short plasma elimination $t_{\frac{1}{2}}$ of ibuprofen. This may provide some explanation for the low risk of upper gastrointestinal toxicity compared with other NSAIDs with longer half-lives. Another line of reasoning stems from the idea of the inactive *R* enantiomer competing with active *S*-ibuprofen for the active binding site on COX-1. It is possible that the *R*-ibuprofen isomer may diminish the expected inhibitory effects of *S*-ibuprofen on COX-1 in the stomach. This prevents *S*-ibuprofen from inhibiting gastric prostaglandin (protectant) production to the extent that would be expected, thereby reducing the risk of ulcers.[9]

There are a number of COX-independent clinical effects attributed to the actions of ibuprofen, some of which may have a bearing on the overall analgesic results. These COX-independent effects are non-enantioselective (i.e. induced by both *R*-ibuprofen and *S*-ibuprofen). Such effects may include inhibition of neutrophil attraction and activation, which contributes in part to the antipyretic effect of ibuprofen.[1] Additionally, NSAIDs in general may infiltrate cell membranes and disrupt the activity of G proteins, thereby interfering with cellular signalling processes.[1]

Clinical studies examining the use of ibuprofen in management of knee osteoarthritis

Some key considerations regarding the conduct and interpretation of clinical trials for pharmacological therapies in OA patients have been reviewed by Buchanan and Kean.[21] Although a well-conducted randomized control trial (RCT) ranks highly in the hierarchy of clinical evidence, care should be taken when attempting to generalise results of possibly unrepresentative study groups to the broader population. There are some common explanations for why a study sample may not adequately represent the broader patient base. Patients who agree to participate in such studies often have different characteristics from those who decline.[22] Additionally, elderly patients with other severe illnesses in addition to OA are often excluded from trials.[23]

Publication bias is also an issue that must be acknowledged with OA therapy RCTs.[24] Trials with negative results are less likely to be published, thus resulting in an inflated view of a treatment's success and possibly a threat to the validity of meta-analyses.[24] One must also be aware of the potentially variable OA diagnostic criteria across studies. Given the lack of a clear diagnostic test for OA, inclusion inconsistency between studies is common.[6] This is likely acceptable in the context of interpreting an individual study (as long as internal consistency is maintained) but poses comparability concerns when looking at multiple studies. An additional consideration is the possible misattribution of pain to the condition of OA. This is most common in studies of hand OA (where carpal tunnel syndrome may be a strong contributor to the assessed pain), but is also a concern in studies of the knee and hip. It is rare that nerve

conduction or EMG tests are done to exclude the possibility of confounding radiculopathy in enrolled subjects.[6,25] Another important issue to take into account is that quantitative analysis of improvement in RCTs deals with the average of treatment groups as a whole, rather than at the level of the individual patient.[6,26] Clinicians must bear this in mind when applying the findings of an RCT to the care of individuals.

Literature retrieval and analysis of trials

In preparing this review, the scope of our analysis was focused on ibuprofen therapy studies in patients with OA of the knee. This is the most common large joint that is affected by OA and is generally the simplest to quantify in terms of pain relief and functionality during clinical trials. The goal was to review and synthesize the findings of studies addressing the efficacy of ibuprofen in the management of knee OA.

The literature was searched thoroughly in duplicate to ensure the inclusion of all relevant studies. A search of PubMed was conducted using the following search terms: 'osteoarthritis AND ibuprofen AND knee' with the limits set to 'RCTs OR clinical trials' and 'human subjects'. This yielded a list of 69 articles, which were then retrieved and their abstracts were screened. Studies were included if they followed the design of a double-blind RCT, they contained a placebo group for comparison, they involved patients with symptomatic OA of the knee, and they employed ibuprofen in at least one treatment group. Similar searches were conducted in the Medline and Embase databases (1950 to present). The reference lists of articles were scanned for the presence of any other relevant studies. Relevant articles were included in the final list, which consisted of 10 studies, to be analysed in full-text. Note: trials limited to the knee that fit our criteria were scarce and so exception was made for studies where the majority of subjects had knee OA (usually > 80% of subjects) but some had hip OA. Upon retrieval and full review, five of these studies were deemed to fit the given criteria and were included in the analysis. Two additional studies identified upon hand-searching of reference lists were included.

Efficacy in knee osteoarthritis

Table 2 lists the relevant randomized controlled trials and selected data examining the efficacy of ibuprofen in treating OA of the knee compared with placebo. The assessments were taken at baseline and then at the indicated follow-up times, and a quantification of improvement is presented for both ibuprofen and placebo groups. Various scales were used and different endpoints assessed, the most common being pain and physical function subscales of the Western Ontario and McMaster University Osteoarthritis Index (WOMAC). The pain and physical function subscales are abbreviated as WOMAC-PS and WOMAC-PFS, respectively,[27] and patient global assessment of disease status is abbreviated as PGADS. A negative change from baseline indicates an improvement in a given endpoint. Dosages are shown in mg/day; in most studies, this dosage is divided equally over three administrations per day (t.i.d).

The studies vary significantly in design, measures and administration protocol. It is thus prudent to examine the various elements of the studies in combination with their tabulated results.

Puopolo *et al.*[28] and Wiesenhutter *et al.*[29] conducted large-scale multi-centre RCTs with three treatment arms (placebo, ibuprofen (2400 mg/day → 800 mg t.i.d) and etoricoxib), employing the highly validated WOMAC pain and physical function subscales, along with the PGADS. Both studies admitted subjects who had both clinical and radiographic evidence of OA, and fit within ARA functional class I-III over the previous six months. Puopolo *et al.*[28] concluded that for each of these primary endpoints ibuprofen was superior to placebo, with statistical significance achieved ($P < 0.002$). In the ibuprofen group, 70.1% of subjects achieved at least minimal clinically important improvement on the WOMAC-PS compared with 55.1% in the placebo group. Clinically important improvement was defined as >15% improvement from baseline on the 100 mm scale used.[28,30] Subjects were assessed at two weeks and twelve weeks after treatment administration, and the results were only provided for the twelve-week point. Wiesenhutter *et al.*,[29] although less thorough in reporting results for each endpoint, showed similar results in support of ibuprofen's significant superiority over placebo ($P < 0.01$). The fact that ibuprofen showed significant efficacy across multiple validated endpoints (WOMAC subscales, PGADS), appears to provide strong evidence for its usefulness in managing OA.[28,29]

In the study by Puopolo *et al.*[28] a greater proportion of the placebo group (18.9%) than the ibuprofen group (7%) dropped out due to lack of efficacy. A similar disproportionate drop-out rate due to lack of efficacy was seen when comparing the placebo and ibuprofen groups in the study by Wiesenhutter *et al.*[29] (29.8% and 14%, respectively). This outcome-dependent drop-out rate raises flags for potential bias and skewed results in both studies. The placebo group efficacies reported in the studies may in fact be inflated due to the drop-out of subjects with poor efficacy.[28,29]

In a number of studies, paracetamol was provided as a rescue medication for unmanaged pain in subjects. The amount of rescue paracetamol required by each group over the course of the study would then be counted and analysed as a secondary endpoint in itself.[28–33] This could provide clues as to the efficacy of a particular treatment. In all studies where

Table 2 Studies examining the efficacy of ibuprofen vs placebo in treatment of knee osteoarthritis

Joint affected	Author/publication year	Intervention	Outcomes at follow-up
Knee or hip (>83% knee)	*Puopolo et al*. (2007) (*n* = 548)[28]		12 weeks mean change from baseline (95% CI) (All outcomes scored on a 100 mm visual analogue scale (VAS))
		Placebo	**WOMAC-PS**: –16.47 (–20.55, –12.40) **WOMAC-PFS**: –13.56 (–17.59, –9.54) **PGADS**: –17.85 (–22.41, –13.29)
		Ibuprofen (2400 mg/day)	**WOMAC-PS**: –24.1 (–27.2, –20.99) **WOMAC-PFS**: –20.09 (–23.87, –17.72) **PGADS: –**25.97 (–29.39, –22.54)
		Statistically significant difference (ibuprofen compared with placebo)?	$P < 0.002$ for all three outcome subscales.
Knee or hip (primarily knee)	Wiesenhutter *et al*. (2005) (*n* = 528)[29]		12 weeks (mean change from baseline)
		Placebo	Only the range of mean changes from baseline were provided for the WOMAC-PS, PFS, and PGADS instruments collectively: Range from: –16.53 to –13.55 Changes specific to each subscale are not reported.
		Ibuprofen	Range from: –26.53 to –22.97 Changes specific to each subscale are not reported.
		Statistically significant difference?	$P < 0.01$ for each outcome measure
Knee (non-prescription dose)	Schiff *et al*. (2004) (*n* = 298)[31]		1 week (mean change from baseline)
		Placebo	Mean symptom score reduced by 20–25% from baseline (0–4 point categorical pain scale). Symptoms measured: pain at rest, pain on passive motion, pain on weight bearing, stiffness after rest, day pain, night pain, 50-foot walk. Each was measured on a 0–4 point categorical pain scale, except the walk which was timed in seconds.
		Ibuprofen (1200 mg/day)	Mean symptom score reduced 30–45% from baseline (0–4 point categorical pain scale). Symptoms measured: pain at rest, pain on passive motion, pain on weight bearing, stiffness after rest, day pain, night pain, fifty-foot walk. Each was measured on a 0–4 point categorical pain scale, except the walk which was timed in seconds.
		Statistically significant difference? (ibuprofen compared to placebo)	Pain at rest: $P = 0.077$ (not significant) Pain on passive motion: $P < 0.05$ Pain on weight bearing: $P < 0.01$ Stiffness after rest: $P < 0.01$ Day pain: $P < 0.01$ Night pain: $P = 0.193$ (not significant) 50-Foot walk time: $P < 0.05$
			6 weeks (mean change from baseline)
Knee or hip	Day *et al*. (2000) (*n* = 323)[32]	Placebo	Outcomes scored on 100 mm visual analogue scale Pain when walking on a flat surface (WOMAC question 1): –18.92 (–23.72 to –14.12) WOMAC-PS: –11.89 (–15.98 to –7.80) WOMAC-PFS: –8.76 (–12.72 to –4.79) PGADS: –10.02 (–14.6 to –5.45)

(Continued)

Table 2 *(Continued)*

Joint affected	Author/publication year	Intervention	Outcomes at follow-up
		Ibuprofen (2400 mg/day)	Outcomes scored on 100 mm VAS Pain when walking on a flat surface (WOMAC question 1): –33.55 (–36.26 to –30.84) WOMAC-PS: –22.89 (–25.21 to –20.58) WOMAC-PFS: –18.06 (–20.3 to –15.82) PGADS: –25.28 (–27.87 to –22.69)
		Statistically significant difference? (Ibuprofen compared with placebo)	$P \leq 0.009$ for all four outcome measures (ibuprofen versus placebo)
			3 weeks after administration (change from baseline)
Hip or knee (36 subjects knee, 20 subjects hip)	Bliddal *et al*. (2000) ($n = 56$)[33] (crossover trial)	Placebo	Pain Visual Analogue Scale (100 mm): 0 mm change from baseline; 95% CI (–3, 4)
		Ibuprofen (1200 mg/day)	Pain Visual Analogue Scale (100 mm) Ibuprofen: –15 mm change from baseline; 95% CI (–23, –7.5)
		Statistically significant difference? (Ibuprofen compared with placebo)	
			1 week after administration
Knee	Sacchetti *et al* (1978) ($n = 24$)[34] (balanced incomplete block design-not a true randomised control trial)	Placebo	Pain scored on 0–4 scale (4 = very severe; 0 = no pain) Daytime pain at rest (baseline): 2.44 ± 0.33 Daytime pain at rest (1 week): 1.81 ± 0.32 Night pain at rest (baseline): 2.56 ± 0.33 Night pain at rest (1 week): 1.94 ± 0.32
		Ibuprofen (900 mg/day)	Pain scored on 0–4 scale (4 = very severe; 0 = no pain) Daytime pain at rest (baseline): 2.75 ± 0.32 Daytime pain at rest (1 week): 1.25 ± 0.28 Night pain at rest (baseline): 3.00 ± 0.30 Night pain at rest (1 week): 1.62 ± 0.31
		Statistically significant difference? (Ibuprofen compared with placebo)	$P < 0.01$ when ibuprofen group compared with placebo group daytime pain improvement. $P < 0.01$ when ibuprofen group compared with placebo group night pain improvement.

this was measured, rescue paracetamol consumption was greater in the placebo group than in the ibuprofen group; however, this difference was only statistically significant in two of the four studies that reported it.[28,33]

Numerous studies have noted a distinct trend whereby the majority of the improvement in all primary endpoints is seen within the first two weeks following administration of treatment.[28,29,32] This improved state is maintained over the remainder of the 12-week follow-ups, with only small further improvement. Thus, it may be fair to compare the results from six-week studies and twelve-week studies, because after the two-week mark there is minimal change and the drug effect seems to have reached its peak potential. However, in the study by Schiff *et al.*[31] follow-up time was only one week, and as such it may not be appropriate to compare efficacy from that study with those of longer duration.

Schiff *et al.*[31] assessed ibuprofen dosages of 1200 mg/day (400 mg t.i.d.) and dealt exclusively with subjects suffering from OA of the knee. Forgoing the use of validated standard scales, such as WOMAC, the study instead assessed seven symptoms on a categorical (0–4) scale at baseline and follow-up, noting the changes in each. The assessed symptoms

include knee joint pain at rest, pain on passive motion, pain on weight bearing, severity of joint stiffness, pain severity the previous day, pain severity the previous night, and time taken to walk 50 feet. The authors noted ibuprofen was clinically effective in managing knee OA, with a 30–45% reduction in mean symptom score versus the placebo group's 20–25% score reduction. However, the authors did not define any threshold for clinical significance. The ibuprofen group achieved statistically significant ($P < 0.05$) improvement over the placebo group on five of the seven symptoms (pain at rest and night pain were exceptions). It is also notable that this trial used OTC dosages (1200 mg/day, i.e. 400 mg t.i.d.) of ibuprofen. The fundamental differences in the trial design and dosages make this study difficult to compare and integrate with the others previously discussed.

The crossover RCT by Bliddal *et al*.[33] also yielded data that shows promise for the efficacy of 1200 mg/day (400 mg t.i.d) ibuprofen in the management of knee OA. Treatment with ibuprofen yielded a 15-mm decrease (improvement) from baseline on a 100-mm pain visual analogue scale. The statistical significance of ibuprofen's treatment effect compared with placebo was high ($P < 0.0001$). However, the study was fraught with questionable methodological elements. There were three treatments (ginger extract, ibuprofen and placebo) and subjects were randomized as to which treatment they would receive first. The RCT involved three consecutive treatment periods, each three weeks in duration. Although there was an initial washout period of one week before commencement of the study, there was no washout period after subjects finished one treatment period and were started on a different treatment. There is significant concern that carry-over effects from the previous treatment periods may skew findings in crossover RCTs (when there is no appropriate wash-out period). Eleven subjects were excluded secondarily from the study analysis, three of whom dropped out due to lack of effect; the study did not note to which group the excluded subjects belonged.[33] This series of concerns should prompt careful consideration when interpreting and synthesizing this study's results with the others. Another crossover clinical trial by Sacchetti *et al*.[34] was performed in 1978 using a balanced incomplete block design, and used a patient-scored (0–4) pain scale to assess daytime and night pain in women with knee OA. The study yielded statistically significant indications of improvement at one week in ibuprofen groups compared with placebo groups ($P < 0.01$) for both day and night pain. Other similar measured outcomes yielded congruent results.[34] However, washout periods were not provided between treatment periods, and sufficient validation was not provided for the measurement scales used; these are important methodological notes that should indicate the need for caution in interpretation.

In addition to the patient-assessed endpoints in the clinical trials presented, there is recent physiological evidence supporting the effectiveness of ibuprofen in treating OA. NSAIDs have often been considered as symptom-modifying drugs with a debatable structural effect in the management of OA. The pathogenesis of OA has been highlighted earlier in the paper, with emphasis on progressive breakdown of the cartilage and synovium in the affected joint. Molecular markers have been identified whose urinary levels reflect turnover of cartilage and synovial tissue. These markers are c-telopeptide fragments of type II collagen (CTX-II) and glucosyl galactosyl pyridinoline (Glc-Gal-PYD), respectively.[35,36] It has been demonstrated that in subjects with knee OA accompanied by prominent inflammation, a group receiving placebo experienced increased levels of these CTX-II and Glc-Gal-PYD urinary markers over the course of 4–6 weeks. In a parallel group, subjects who were treated with 2400 mg/day of ibuprofen, levels of urinary CTX-II and Glc-Gal-PYD over the same period of time did not rise as much. These results indicate that ibuprofen may help prevent the high rate of cartilage and synovium catabolism characteristic of OA progression.[37]

Topical ibuprofen

While this review has addressed the pharmacokinetics and clinical efficacy of only oral formulations of ibuprofen, another common method of administration is in the form of topical creams or gels, especially in treatment of knee OA. Trnavsky *et al*.[38] and Rovensky *et al*.[39] examined topical administration of 5% ibuprofen cream for treatment of knee OA in double-blind, placebo controlled RCTs and concluded that topical ibuprofen's efficacy is clinically and statistically relevant compared with placebo cream. These studies have been confirmed in a series of studies and evaluations by Underwood's group.[40–44] In essence, the conclusions from these large-scale evaluations in the general practice setting in southern England are that topical ibuprofen for knee OA, especially long term, has advantages over oral ibuprofen in that there are fewer side effects.

Discussion

The above studies present evidence for the efficacy of ibuprofen compared with placebo in the management of knee OA. Both statistical significance and clinical significance (where defined and reported) were achieved in terms of improvement on the highly validated and widely accepted WOMAC subscales. Certainly, however, a much broader and more clinically holistic set of factors must be taken into account when deciding which treatment to employ for an individual patient. RCTs and other clinical studies focus on means and medians rather than clinical relevance to the unique individual patient (understandably so, given the statistical power and large sample sizes used). Thus, the limits of evidence-based medicine become apparent and clinicians must use

their expertise to apply the evidence in the context of the patient sitting before them.[45,46]

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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