An Overview of Clinical Pharmacology of Ibuprofen

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Abstract:

Ibuprofen was the first member of Propionic acid derivatives introduced in 1969. It is a popular domestic and over the counter analgesic and antipyretic for adults and children. Ibuprofen has been rated as the safest conventional NSAID by spontaneous adverse drug reaction reporting systems in the UK. This article summarizes the main pharmacological effects, therapeutical applications and adverse drug reactions, drug-drug interactions and food drug interactions of ibuprofen that have been reported especially during the last 10 years.

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Introduction

Ibuprofen is (2RS)-1[4-(2-methyl propyl) phenyl] propionic acid (BP. 2004). Ibuprofen was the first member of propionic acid derivatives to be introduced in 1969 as a better alternative to Aspirin. Gastric discomfort, nausea and vomiting, though less than aspirin or indomethacin, are still the most common side effects.[1]

Ibuprofen is the most commonly used and most frequently prescribed NSAID.[2,3] It is a non-selective inhibitor of cyclo-oxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2).[4] Although its anti inflammatory properties may be weaker than those of some other NSAIDs, it has a prominent analgesic and antipyretic role. Its effects are due to the inhibitory actions on cyclo-oxygenases, which are involved in the synthesis of prostaglandins. Prostaglandins have an important role in the production of pain, inflammation and fever.[5]

Clinical Pharmacology of Ibuprofen

Ibuprofen is supplied as tablets with a potency of 200 to 800 mg.[6] The usual dose is 400 to 800 mg three times a day.[7] It is almost insoluble in water having pKa of 5.3.[8] It is well absorbed orally; peak serum concentrations are attained in 1 to 2 hours after oral administration. It is rapidly bio-transformed with a serum half life of 1.8 to 2 hours. The drug is completely eliminated in 24 hours after the last dose and eliminated through metabolism.[9,10] The drug is more than 99% protein bound, extensively metabolized in the liver and little is excreted unchanged.[11]

Although highly bound to plasma proteins (90-99%), displacement interactions are not clinically significant, hence the dose of oral anti-cogulants and oral hypoglycemic needs not be altered.[1] More than 90% of an ingested dose is excreted in the urine as metabolites or their conjugates, the major metabolites are hydroxylated and carboxylated compounds.[6,12]

Old age has no significant effects on the elimination of ibuprofen.[13] Renal impairment also has no effect on the kinetics of the drugs, rapid elimination still occur as a consequence of metabolism.[14] The administration of ibuprofen tablets either under fasting conditions or immediately before meals yield quiet similar serum concentrations-time profile. When it is administered immediately after a meal, there is a reduction in the rate of absorption but no appreciable decrease in the extent of absorption.[15]

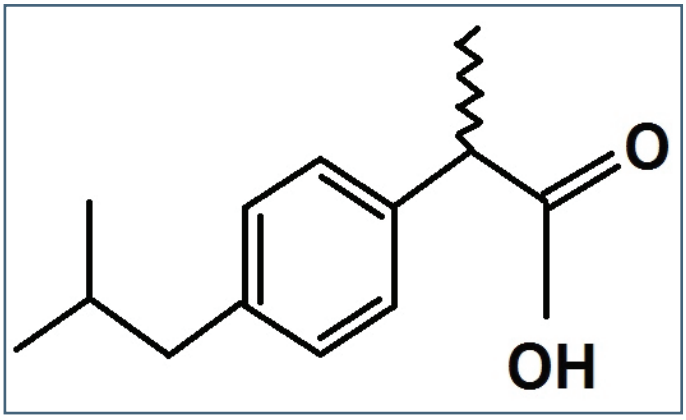

Figure 1: Structural formula of ibuprofen

Therapeutic Applications

A low dose ibuprofen is as effective as aspirin and paracetamol for the indications normally treated with over the counter medications.[16] It is widely used as an analgesic, an anti inflammatory and an antipyretic agent.[17-19] Recemic ibuprofen and S(+) enantiomer are mainly used in the treatment of mild to moderate pain related to dysmenorrhea, headache, migraine, postoperative dental pain, management of spondylitis, osteoarthritis, rheumatoid arthritis and soft tissue disorder.[20] A number of other actions of NSAIDs can also be attributed to the inhibition of prostaglandins (PGs) or thromboxane synthesis, including alteration in platelet function

(PGI2 and Thromboxane), prolongation of gestation and labor (PGE2, PGF2A), gastrointestinal mucosal damage (PGI2 and PGE2), fluid and electrolyte imbalance (renal PGs), premature closure of ductus arteriosus (PGE2) and bronchial asthma (PGs).[21] The main therapeutic applications of ibuprofen are as follows:

Patent Ductus arterosus (PDA)

This is a frequent complication in premature infants. So far, intravenous indomethacin is the standard mode of medical therapy.[22] However, because of adverse effects of indomethacin, other PG inhibitors such as ibuprofen have been studied for the closure of ductus arteriosus, and results indicated that ibuprofen is as effective as indomethacin.[23]

Rheumatoid and osteo-arthritis (RA and OA)

Ibuprofen is widely used in the management of numerous inflammatory, musculoskeletal and rheumatic disorders, because they are highly effective having minimal toxicities.[24,25] Ibuprofen 2400 mg per day resulted in rapid improvement and complete resolution of gouty arthritis within 72 hours.[26] In doses of approximately 2400 mg daily, it is equivalent to 4g of aspirin in terms od anti inflammatory effects.[27] Higher doses, 1200 to 1600 mg per day have been compared with a number of NSAIDs and it has been found to be as effective and well tolerated.[28] Osteoarthritis is very common and treatment involves NSAIDs, particularly ibuprofen.[29,30] For control of joint symptoms, diclofenac, ibuprofen, tolmetin and naproxen are equally effective.[31] Roughly 1% of rheumatoid arthritis (RA) patients receiving NSAIDs are prone to develop major GI bleeds.[32] With ibuprofen, gastric toxicity has been observed in 10 - 32% of patients.[33]

Table 1: Doses of Ibuprofen in adult & Children (34)

Patients	Ibuprofen	Doses
Adult	Analgesia	200-400 mg, Every 4-6 hrs
	Anti-inflammatory	300 mg, Every 6-8 hrs or 400-800 mg 3-4 times daily
Children	Anti pyretic	5-10 mg/kg. Every 6 hrs (max. 40 mg/kg per day)
	Anti-inflammatory	20-40 mg/kg/day in 3-4 divided dose

Cystic fibrosis (CF)

High dose ibuprofen therapy has also been shown to be effective in decreasing inflammation, probably by decreasing polymorphonuclear cell influx into the lungs.[34] The risk of developing GI side effects from high dose ibuprofen therapy is low in patients with CF.[35,36]

Orthostatic hypotension

Ibuprofen is useful in the treatment of severe orthostatic hypotension as with other NSAIDs.[37] Toxic effects are unlikely at doses below 100 mg/kg but can be life-threatening or severe above 400 mg/kg.[38] However, large doses do not indicate that the clinical course is likely to be lethal.[39]

Dental pain

Ibuprofen is one of the most effective and widely used NSAID in treatment of dental pain.[40] Dental practitioners have relied on ibuprofen and other NSAIDs to manage acute and chronic orofacial pain.[41] A dose of 400 mg of ibuprofen provides effective analgesic for the control of postoperative pain after third molar surgery.[42] A liquid gel preparation of ibuprofen 400mg provides faster relief and superior overall efficacy in post surgical dental pain.[27]

Dysmenorrhea, fever and headache

Non-prescription ibuprofen is useful for managing minor aches and pains, reducing fever and relieving symptoms of dysmenorrhea.[43-45] Dysmenorrhea is the most common menstrual complain.[46] Ibuprofen was superior to placebo for pain relief and menstrual fluid PGF2 alpha suppression.[47] Cycloxygenase inhibitors reduce the amount of menstrual prostanoids release, with concomitant reduction in uterine hyper contractility.[48] Over-the-counter (OTC) ibuprofen preparations are mainly used for acute indications, such as fever or headaches, especially tension type headache.[49-51]

It has been reported that the combined use of paracetamol and ibuprofen reduce fever very rapidly.[52] Fever almost invariably accompanies uncomplicated falciparum malaria. In a randomized double-'blind' study, a single dose of ibuprofen was compared with paracetamol for the treatment of fever >38·5 °C due to uncomplicated falciparum malaria. Ibuprofen was significantly more effective than paracetamol in lowering temperatures throughout the first 4-5 hrs after dosing and thus should be considered as an antipyretic agent in the management of uncomplicated falciparum infections, providing there is no contraindication to its use.[53] Evers et al. in 2006, conducted a double blind study to investigate the efficacy of zolmitriptan and ibuprofen in the treatment of migraine in children and adolescents. Pain relief rates after two hours were 28% for placebo, 62% for zolmitriptan and 69% for ibuprofen.[54]

Prophylaxis of Alzheimers disease

The administration of NSAIDs, particularly ibuprofen markedly reduced neurodegeneration.[55,56] In some studies, ibuprofen showed superior results compared to placebo in the prophylaxis of Alzheimer's disease, when given in low doses over a long time.

Further studies are needed to confirm the results before ibuprofen can be recommended for this indication.[57]

Parkinson's disease (PD)

Inflammation and oxidative stress have been implicated as pathogenic mechanisms in PD.[58] Epidemiologic evidence showed that regular use of NSAIDs, particularly non aspirin COX inhibitors such as ibuprofen lower the risk of PD.[59,60] It induced apoptosis significantly in early and late stages, suggesting that these anti-inflammatory agents might inhibit microbial proliferation.[61]

Breast cancer

Harris et al. in 1999 conducted a study for utilization of NSAIDs in breast cancer. Breast cancer rate was decreased by approximately 50% with regular ibuprofen intake and 40% with regular aspirin intake. Results suggested that specific NSAIDs may be effective chemo preventive agents against breast cancer.[62]

Adverse Reactions

NSAIDs are widely used, frequently taken inappropriately and potentially dangerously.[63] Nevertheless, ibuprofen exhibits few adverse effects.[64] The major adverse reactions include the affects on the gastrointestinal tract (GIT), the kidney and the coagulation system.[65] Based on clinical trial data, serious GIT reactions prompting withdrawal of treatment because of hematemesis, peptic ulcer,[66] and severe gastric pain or vomiting showed an incidence of 1.5% with ibuprofen compared to 1% with placebo and 12.5% with aspirin.[67] Ibuprofen was a potential cause of GI bleeding,[68,69] increasing the risk of gastric ulcers and damage, renal failure, epistaxis,[70-73] apoptosis,[74] heart failure, hyperkalaemia,[75] confusion and bronchospasm.[76] It has been estimated that 1 in 5 chronic users (lasting over a long period of time) of NSAIDs will develop gastric damage which can be silent.[77]

Other adverse effects of ibuprofen have been reported less frequently. They include thrombocytopenia, rashes, headache, dizziness, blurred vision and in few cases toxic amblyopia, fluid retention and edema. Patients who develop ocular disturbances should discontinue the use of ibuprofen.[78] Effects on kidney (as with all NSAIDs) include acute renal failure, interstitial nephritis, and nephritic syndrome, but these very rarely occur.[27]

Drug-Drug Interactions

Ibuprofen has established drug interactions with NSAIDs which are both pharmacokinetic or pharmacodynamic in origin.[79,80] The most potentially serious interactions include the use of NSAIDs with lithium, warfarin, oral hypoglycemics, high dose methotrexate, antihypertensives, angiotensin converting enzyme inhibitors, ß-blockers, and diuretics. Anticipation and care full monitoring can often prevent serious events when these drugs are used concomitantly.[81]

Observational studies and in-vivo experiments have raised concerns that the cardio protective effects of taking *aspirin* are blocked by ibuprofen which competitively inhibits aspirin's binding sites on platelets.[82-85] The pharmacodynamic interactions of aspirin and ibuprofen may not have a significant impact on patient outcomes.[86] Palmer et al. in 2003 suggested that NSAIDs interfere with certain antihypertensive therapies. Ibuprofen caused a significant increase in systolic and diastolic blood pressure compared to placebo.[87] A case of life-threatening hypotension due to sinus arrest was described in a patient in whom exercise-induced hyperkalemia developed during a stable regimen that included verapamil, propranolol, and ibuprofen.[88] Similar to other NSAIDs, ibuprofen is likely to decrease the diuretic and anti hypertensive actions of thiazides, furosemide and ß-Blockers.[1]

Hence the administration of ibuprofen caused a significant decrease in urinary output, inulin clearance, sodium excretion, osmolar clearance, free water clearance and urinary PGE2 clearance.[89]

Many overdose experiences have been reported in medical literature.[90] The maximum daily dose for ibuprofen is 3200 mg. Ibuprofen may cause serious toxicity when overdosed, mainly in children on ingestion of 400 mg/kg or more. The symptoms of high dose include seizures, apnea, and hypertension, as well as renal and hepatic dysfunction.[90-93] Ibuprofen has been implicated in elevating the risks of myocardial infraction, particularly among those chronically using high doses.[94-98]

Desmopressin and NSAIDs should not be used in combination in patients with bleeding disorders.[99] Coadministration of *thiopurines* and various NSAIDs (ketoprofen and ibuprofen) may lead to drug interactions.[100]

It has been observed that caffeine improves antinociceptive efficacy of some non-steroidal anti inflammatory drugs (NSAIDs) in several experimental models, however, these effects have been questioned in humans. Caffeine is able to potentiate the antinociceptive effect of ibuprofen. This effect was greater than the maximum produced by morphine in the experimental conditions.[101] Caffeine also enhances the effectiveness of most analgesics, including ibuprofen. Comparison of the cumulative response scores revealed a trend toward a greater response to ibuprofen-caffeine treatment of headaches.[102]

Gemfibrozil moderately increases the AUC of R-ibuprofen and prolongs its t (1/2), indicating that R-ibuprofen is partially metabolised by Cytochrome P2C8 (CYP2C8). The interconversion

of R- to S-ibuprofen can explain the small effect of gemfibrozil on the t (1/2) of S-ibuprofen. However, the gemfibrozil-ibuprofen interaction is of limited clinical significance.[103]

St. John's wort is a popular herbal supplement that has been involved in various herb-drug interactions. St. John's wort treatment appears to significantly reduce the mean residence time of S-ibuprofen, no ibuprofen dose adjustments appear warranted when the drug is administered orally with St. John's wort, due to the lack of significant changes observed in ibuprofen area under the curve (AUC) and maximum concentration C (max) for either enantiomer.[104]

The effects of the antifungals *voriconazole and fluconazole* on the pharmacokinetics of S-(+) - and R-(-)-ibuprofen were studied by Hynninen et al. A reduction of ibuprofen dosage should be considered when ibuprofen is coadministered with voriconazole or fluconazole, especially when the initial ibuprofen dose is high due to the inhibition of the cytochrome P450 2C9-mediated metabolism of S-(+)-ibuprofen.[105]

The competitive binding characteristics of ibuprofen and *naproxen* with respect to the binding site on bovine serum albumin (BSA) were studied. Ibuprofen displaced naproxen and vice versa from its high affinity binding site (site II) and the displaced drug rebound to its low affinity binding site (site I) on BSA molecule.[106]

Anandamide, an endocannabinoid, is degraded by the enzyme fatty acid amide hydrolase which can be inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs). The antinociceptive interaction between anandamide and ibuprofen was synergistic. The combination of anandamide with ibuprofen produced synergistic antinociceptive effects involving both cannabinoid CB_1 and CB_2 receptors.[107]

A study by Kaminski et al. in 1998 showed that all NSAIDs enhanced the protective activity of *valproate magnesium* against maximal electroshock-induced seizures. Only ibuprofen and piroxicam enhanced the anticonvulsive activity of diphenylhydantoin. Ibuprofen also decreased the effective dose 50 (ED_{50}value) of valproate (for the induction of motor impairment). Thus, NSAIDs could enhance the protective activity of antiepileptics.[108]

Food-Drug Interaction

The absorption of ibuprofen and oxycodone when given as a combination tablet was affected by the concomitant ingestion of food. Food intake before the administration of a single dose of the combination did not affect ibuprofen absorption but marginally increased the extent, but not the rate, of oxycodone absorption.[109] The effect of food on the plasma concentration-time profile of sustained release dosage forms of ibuprofen has been investigated after an overnight fast or along with a heavy vegetarian breakfast. The formulation exhibited multiple peaks on the plasma concentration-time curve. Although food did not affect the bioavailability of ibuprofen, there was a statistically significant increase in the mean concentration. Results indicated that while qualitative changes in the plasma concentration versus time curves are primarily influenced by the nature of the formulation and the type of meal, bioavailability is influenced by the absorption characteristics of the drug as well.[110]

The Cmax and AUC0-alpha of ibuprofen were significantly increased after a single and multiple doses of Coca-Cola, thereby indicating an increased extent of absorption of ibuprofen. The daily dosage and frequency of ibuprofen must be reduced when administered with Coca-Cola.[111] Garba et al. in 2003 conducted a study indicating that Tamarindus indica fruit extract significantly increased the bioavailability of Ibuprofen.[112]

Warnings

The use of OTC products containing aspirin, acetaminophens, ibuprofen, naproxen or ketoprofen may increase the risk of hepatotoxicity and gastrointestinal hemorrhage in individuals who consume three or more alcoholic drinks daily.[113]

Tamburini et al. have reported an atypical presentation of meningitis due to Neisseria meningitidis in a patient who received large doses of ibuprofen. Anti-inflammatory therapy such as NSAIDs could reduce CSF inflammation and modify the clinical outcome in patients with bacterial meningitis. However, the use of NSAIDs is not recommended in bacterial meningitis due to a lack of studies.[114]

Ibuprofen may exacerbate severe asthma. With this perception, ibuprofen was administered for postoperative pain management to a 17-year-old boy with allergic rhinitis and previous severe asthma (at a time when well controlled), who then had a severe asthma exacerbation.[115] Also, it has been reported that gastrointestinal tract anatomical abnormalities or dysmotility may be contraindications for therapy with high-dose ibuprofen in patients with cystic fibrosis.[35]

A closer look at the nonprescription analgesics revealed their potential harm when used by solid-organ transplant recipients.[116] Excretion into breast milk is thought to be minimal, however it should be used with caution by women who are breast feeding.[78]

Conclusion

Ibuprofen is suitable for self medication with regards to its relatively wide spectrum of indication, good tolerance and safety.[117] Overall, it has been rated as the safest conventional NSAID by the spontaneous

adverse drug reaction reporting system in the United Kingdom.[1]

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