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Pristina, Kosovo 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

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

Therapeutic Applications

A low dose ibuprofen is as effective as aspirin and paracetamol for the indications normally treated with over the counter medications. It is widely used as an analgesic, an anti inflammatory and an antipyretic agent. 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. 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).16

For the relief of primary dysmenorrhea, ibuprofen therapy should be started with the earliest onset of pain ... 17
Ibuprofen is a commonly used nonsteroidal antiinflammatory (NSAID) drug which is available both by prescription and over-the-counter. Ibuprofen is considered to be among the safest NSAIDs and is generally well tolerated but can, nevertheless, rarely cause clinically apparent and serious acute liver injury. 18
The main therapeutic applications of ibuprofen are as follows:

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. Ibuprofen 2400 mg per day resulted in rapid improvement and complete resolution of gouty arthritis within 72 hours. In doses of approximately 2400 mg daily, it is equivalent to 4g of aspirin in terms od anti inflammatory effects. 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. Osteoarthritis is very common and treatment involves NSAIDs, particularly ibuprofen. For control of joint symptoms, diclofenac, ibuprofen, tolmetin and naproxen are equally effective. Roughly 1% of rheumatoid arthritis (RA) patients receiving NSAIDs are prone to develop major GI bleeds. With ibuprofen, gastric toxicity has been observed in 10 - 32% of patients.

Table 1

Doses of Ibuprofen in adult & Children

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. The risk of developing GI side effects from high dose ibuprofen therapy is low in patients with CF.

Dental pain

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

Dysmenorrhea, fever and headache

Non-prescription ibuprofen is useful for managing minor aches and pains, reducing fever and relieving symptoms of dysmenorrhea. Dysmenorrhea is the most common menstrual complain. Ibuprofen was superior to placebo for pain relief and menstrual fluid PGF2 alpha

suppression. Cycloxygenase inhibitors reduce the amount of menstrual prostanoids release, with concomitant reduction in uterine hyper contractility. Over-the-counter (OTC) ibuprofen preparations are mainly used for acute indications, such as fever or headaches, especially tension type headache.

It has been reported that the combined use of paracetamol and ibuprofen reduce fever very rapidly. 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. 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.

Prophylaxis of Alzheimers disease

The administration of NSAIDs, particularly ibuprofen markedly reduced neurodegeneration. 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.

Parkinson's disease (PD)

Inflammation and oxidative stress have been implicated as pathogenic mechanisms in PD. Epidemiologic evidence showed that regular use of NSAIDs, particularly non aspirin COX inhibitors such as ibuprofen lower the risk of PD. It induced apoptosis significantly in early and late stages, suggesting that these anti-inflammatory agents might inhibit microbial proliferation.16

23.

24.

25. Adverse Reactions

NSAIDs are widely used, frequently taken inappropriately and potentially dangerously.19 Nevertheless, ibuprofen exhibits few adverse effects.20 The major adverse reactions include the affects on the gastrointestinal tract (GIT), the kidney and the coagulation system.21 Based on clinical trial data, serious GIT reactions prompting withdrawal of treatment because of hematemesis, peptic ulcer,22 and severe gastric pain or vomiting showed an incidence of 1.5% with ibuprofen compared to 1% with placebo and 12.5% with aspirin.23 Ibuprofen was a potential cause of GI bleeding,24·25 increasing the risk of gastric ulcers and damage, renal failure, epistaxis,26 apoptosis,27 heart failure, hyperkalaemia,28 confusion and bronchospasm.29 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.30

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. Effects on kidney (as with all NSAIDs) include acute renal failure, interstitial nephritis, and nephritic syndrome, but these very rarely occur.16

Drug-Drug Interactions

Ibuprofen has established drug interactions with NSAIDs which are both pharmacokinetic or pharmacodynamic in origin.31 The most potentially serious interactions include the use of NSAIDs with lithium, warfarin, oral hypoglycemics, high dose methotrexate, antihypertensives, angiotensin converting enzyme inhibitors, β-blockers, and diuretics. Anticipation and care full monitoring can often prevent serious events when these drugs are used concomitantly.32

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.33 The pharmacodynamic interactions of aspirin and ibuprofen may not have a significant impact on patient outcomes.34 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.35 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.36 Similar to other NSAIDs, ibuprofen is likely to decrease the diuretic and anti hypertensive actions of thiazides, furosemide and β-Blockers.1

Many overdose experiences have been reported in medical literature. 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.37 Ibuprofen has been implicated in elevating the risks of myocardial infraction, particularly among those chronically using high doses.38

Desmopressin and NSAIDs should not be used in combination in patients with bleeding disorders.39Coadministration of thiopurines and various NSAIDs (ketoprofen and ibuprofen) may lead to drug interactions.40

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.41 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.42

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.43

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.44

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.45

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.46 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.47
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.48 Garba et al. in 2003 conducted a study indicating that Tamarindus indica fruit extract significantly increased the bioavailability of Ibuprofen.49

Warnings

The use of OTC products containing aspirin, acetaminophens, ibuprofen, naproxen or ketoprofen may increase the risk of hepato-toxicity and gastrointestinal hemorrhage in individuals who consume three or more alcoholic drinks daily.50
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.51
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.52 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.16
A closer look at the nonprescription analgesics revealed their potential harm when used by solid-organ transplant recipients.53 Excretion into breast milk is thought to be minimal, however it should be used with caution by women who are breast feeding. 16

Ibuprofen should be used with caution in patients with peptic ulcer disease, GI perforation or bleeding, bleeding abnormalities (especially in patients who may be adversely affected by prolongation of bleeding time), impaired renal function, hypertension, or compromised cardiac function. 54

Ibuprofen is not recommended for use by pregnant women, or by those who are breast-feeding their infants. 55

Purpose

Since the use of analgesics is more commonly used in Kosovo, where you can get them even without a doctor's prescription, we set out a task to see how young people are using Ibuprofen.

The purpose of this paper is to compare the use of Ibuprofen as an analgesic with other non-steroidal anti-inflammatory drugs and to see young people's knowledge of its use.

Material and methods

The study involved 117 youth. Their knowledge of the use of analgesics is analyzed. Of the 117 youth, 76.1% were female, while 23.9% were male. The youngest was 17 and the oldest was 32.
The young people who attended were students of the University for Business and Technology. The students who attended were mostly from Faculty of Nursing then Dentistry, Pharmacy, Architecture, and fewer other.
The students were subjected to an online survey, which asked questions about the use of Ibuprofen.

Results

Of the students who participated, 76.1% were female, and 23.9% were male.
The most commonly used drugs were Paracetamol with 38.05%, followed by Ibuprofen with 31.34%, Ketoprofen with 14.92%, Nimesulid with 4.47% and Diclofen with 3%. 5.22% responded that they did not take any medication for pain while 3% of the youth did not know what medication they used for pain. Of these, 82.1% were aware that Ibuprofen was analgesic and antipyretic, while only 74.5% used it in case of pain and fever. When asked for what pain they used ibuprofen, 46.25% responded to headache, 26.53% for menstrual pain, 8.85% for muscular pain also 8.85% for bone pain, 2.72% for toothache and 6.80% said they had never used Ibuprofen.
Although allergic reactions to Ibuprofen are one of the most common causes of drug allergy, only 0.9% responded that were allergic. They showed that 76.9% of them use Ibuprofen without a doctor's prescription, while those who use it with a doctor's prescription 70.1% follow the doctor's advice on how to use it.
Of the young people questioned about the side effects after using Ibuprofen 13.7% answered that they had side effects. The most common side effects were stomach pain, nausea, fatigue while less headache, muscle tightness, constipation, dizziness, depression. Ibuprofen use had effect at 82.9%, 15.4% did not know it if it was effective and to 1.7% did not have effect. Ineffectiveness may be a consequence of not receiving advice from a doctor or pharmacist, or even not reading a prescription, with only 36.8% responding that they read it.
The pharmaceutical form of Ibuprofen most commonly used by young people is in the form of tablets 70.9%, 12.8% in powder form, and less so in other forms such as dragees, capsules or even syrups.
The most commonly used dose is 400mg 31.6%, 200mg 27.4%, 600mg 11.1%, 800mg 0.9%, while the rest did not know the dose they used. The study found that 86.3% had no tolerance to Ibuprofen.
Finally, 75.9% of young people said that they would recommend Ibuprofen for use, while 24.1% would not recommend it.

Conclusion

These findings can be drawn from the analysis of young people's use and knowledge of Ibuprofen.

1. Although the results showed that Paracetamol is more commonly used by young people, Ibuprofen use is still high compared to other analgesics.
2. Most young people were aware that Ibuprofen is analgesic and antipyretic.
3. The reason young people used Ibuprofen was headache, menstrual cramps and less other pain.
4. Only a very small percentage turned out to be allergic to Ibuprofen.
5. Results showed that many young people use Ibuprofen without a doctor's prescription.
6. Ibuprofen has had an effect on most of its users.
7. Side effects appeared in a small number of young people, with the most common side effects being stomach pain, fatigue, headaches and fewer other side effects.
8. The use of Ibuprofen has had a positive effect on most users.
9. Tolerance to Ibuprofen has gained only a small percentage.
10. The most commonly used pharmaceutical form of Ibuprofen turned out to be the tablet form, then the powder form, to a lesser extent the other forms.
11. Ibuprofen is used for certain purposes in young people, and there have been no cases of overdose. The most commonly used dose is 400mg.

Based on the results presented and the conclusion of this paper we can suggest that Ibuprofen is a safe drug for use, the side effects are not very noticeable in young people, and the participants used Ibuprofen for certain purposes.

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