Structure and properties of ibuprofen

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Ibuprofen, which is a member of the propionic acid group of Non-steroidal anti-inflammatory, drugs (NSAIDs). Ibuprofen is a racemic mixture of [+]S- and [-]R-enantiomers. Ibuprofen contains contains a stereocenter in the α-position of the propionate moiety. Studies shown that [+]S -ibuprofen was the active form and it showed activity in both in-vivo and in-vitro.

Ibuprofen is white to off-white in colour and occurs as a crystalline powder, with a melting point of 74° to 77°C. It is practically insoluble in water, but readily soluble in organic solvents such as ethanol and acetone. Ibuprofen has a pKa value of 4. 43±0. 03 and an n-octanol/water partition coefficient of 11. 7 at pH 7. 4. The chemical name for ibuprofen is (±)-2-(p-iso-butylphenyl) propionic acid. The molecular weight of ibuprofen is 206. 28. Its molecular formula is C13H1802.

Mechanism of action

The major action of Ibuprofen and all other Non-steroidal anti-inflammatory drugs and is the inhibition of the cyclooxygenase enzyme or the COX enzymes and hence inhibiting the synthesis of prostaglandins. These cyclooxygenase enzymes catalyse the reaction of synthesis of prostaglandins and thromboxanes from arachidonic acid, which in turn is synthesized from phospholipids by the action of the phospholipase enzyme. The prostaglandins and thromboxanes are then responsible for the synthesis of various inflammatory mediators. There are two types of cyclooxygenase enzymes namely, cyclooxygenase enzyme-I (COX-I) and cyclooxygenase enzyme-II (COX-II). COX-I is a constitutive enzyme which is released in most of the body tissues including the blood platelets. COX-I performs a house-keeping role in the body and is involved in the tissue homeostasis. Whereas, COX-II is present in the inflammatory cells and is responsible for the production of prostanoid mediators, which are responsible for inflammation, pain and fever. Therefore, inhibition of the COX-II leads to the anti-inflammatory, anti-pyretic and analgesic activity of ibuprofen and whereas on the other hand, inhibition of COX-II is responsible for the unwanted effects of ibuprofen in the gastric mucosa and on platelet aggregation.

In 2002, a study reported that, ibuprofen selectively inhibits a new variant of the COX enzyme that was totally different from the then known two variants of cyclooxygenase enzymes, the COX-I and COX-II. This iso-enzyme is now referred as the COX-III enzyme. Study also showed that this COX-III enzyme was only expressed in the brain and in the spinal cord. Its exact mechanism and actions is still poorly understood, but future

research may provide further insight into how it works. A study on rats has shown that administration of ibuprofen increases the bioavailability of serotonin (5-HT) in rats and evidence for a similar mechanism in humans was also found. Chronic ibuprofen doses in rat showed down-regulation of central 5-HT2A receptors and an increase in the number of serotonin transporter proteins.

In 2006, a study showed that ibuprofen is converted to N-arachidonoyl phenolamine, or AM404, a compound known as an endogenous cannabinoid reuptake inhibitor and it indirectly activates the CB-I cannabinoid receptor, resulting in analgesia. This activity was proven through the induction of a CB-I receptor antagonist which resulted in the reversal of the analgesic action of ibuprofen.

Pharmacokinetics

Absorption

Ibuprofen is well absorbed from the gastro intestinal tract. The peak plasma level of ibuprofen is reached within 1 to 2 hours. It was shown in a study that absorption of ibuprofen is faster in fasting conditions. Food affects the rate of absorption of ibuprofen but the extent of absorption remains unchanged. The study also showed that, ibuprofen when administered with food delays the time taken for peak plasma concentration by approximately 30-60 minutes.

Distribution

Ibuprofen like the other agents of its class is highly protein bound. It was found in a study that about 90-99% of ibuprofen was protein bound at a

concentration of 20µg/ml and this binding was non-linear. The volume of distribution ibuprofen changes with age and fever conditions. Studies reveal that febrile children’s less than 11 years old have volume of distribution approximately 0. 2 L/kg, while adults have volume of distribution approximately 0. 12 L/kg.

Metabolism

Ibuprofen is extensively metabolised in the liver to form inactive metabolic compounds. Ibuprofen is mainly metabolised by glucoronidation reaction. A study showed that majority of the ibuprofen dose was recovered in the urine as hydroxy phenyl propionic acid (25%) and carboxy propyl phenyl propionic acid (37%) metabolites.

Elimination

Ibuprofen and its inactive metabolites are rapidly and completely excreted by the kidney. About 95% of the administered dose of ibuprofen is eliminated in the urine. The elimination half-life of ibuprofen is in the range of 1. 9 hours to 2 hours.

Pharmacological activity

Ibuprofen has the following pharmacological actions on the biological system

Antipyretic effect

Analgesic effect

Anti-inflammatory effect

Antipyretic effect

A normal body temperature is regulated by a centre in the hypothalamus that ensures a balance between heat loss and heat production in the body. Therefore, the hypothalamus maintains a normal temperature of the body and thus it acts as a thermostat. When there is a disturbance in this hypothalamic thermostat, temperature of the body set by the hypothalamus is raised, fever occurs. Ibuprofen and other Non-steroidal anti-inflammatory drugs reset this rise in the temperature. It regulates various temperature regulatory mechanisms such as dilation of superficial blood vessels, sweating etc. to reduce the temperature. Ibuprofen and other NSAID’s do not affect the normal temperature.

Ibuprofen and other NSAID’s are thought to act as antipyretic agents by inhibiting the prostaglandin production in the hypothalamus. During an inflammatory reaction, the bacterial endotoxins cause a release of a pyrogen-IL-1 from macrophages. This release of pyrogen stimulates the generation of E-type prostaglandins in the hypothalamus, this in turn causes the elevation of temperature. There are evidences that prostaglandins are not the only mediators of fever, hence ibuprofen and other NSAID’s may have some alternate mechanisms for their antipyretic activity which is not yet known.

Analgesic effect

Ibuprofen is mainly effective against pain associated with inflammation or tissue damage. This is due to the inhibition of prostaglandins that sensitise nociceptors to inflammatory mediators such as bradykinin. Therefore

ibuprofen is effective against pains that are associated with increased prostaglandin synthesis. Their ability to relieve headache may be related to the inhibition of the vasodilator effect of prostaglandins on the cerebral vasculature. There are some evidences that ibuprofen have a central effect by an action mainly in the spinal cord where it inhibits the COX-III enzyme. This action of ibuprofen is not yet clearly known.

Anti-inflammatory activity

Many chemical mediators are released when there is a stimulus of an inflammatory and allergic response. This response leads to vasodilation, increased vascular permeability, cell accumulation, etc., which are produced by several mechanisms. Furthermore, different mediators may be of particular importance in different inflammatory and allergic conditions. Ibuprofen reduces mainly those components of the inflammatory and immune response in which mediators produced by COX-II enzyme action plays a significant part. The components inhibited by ibuprofen are vasodilation, oedema and pain. Ibuprofen has no effect on those processes which contribute to tissue damage as in chronic inflammatory conditions such as rheumatoid arthritis, vasculitis and nephritis.

Uses of ibuprofen

Ibuprofen is used to treat a wide range of illnesses such as headaches, backache, menstrual cramps, dental pain, neuralgia, rheumatic pain, muscular pain, migraine, arthritis and athletic injuries. Ibuprofen is also used to reduce fever and to relieve minor aches and pain caused due to common cold or flu.

In a recent study, it was found that ibuprofen was effective in the treatment of Alzheimer's disease when given in low doses over a long period of time. A study also showed that ibuprofen is associated with a lower risk of Parkinson's disease, and ibuprofen may help in delaying and prevent it.

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Adverse effects of Ibuprofen

Ibuprofen appears to have the lowest incidence of adverse drug reactions (ADR's) when compared to all other non-selective NSAID's. However, this only holds true at lower doses of ibuprofen. Common adverse effects of ibuprofen with the gastrointestinal tract include – nausea, dyspepsia, heartburn, gastrointestinal ulceration and bleeding, diarrhoea, loss of appetite, stomach pain. Effects on central nervous system include headache, dizziness, fatigue and nervousness. Hypersensitivity reactions include skin rashes, itching. In very rare cases ex-foliative dermatitis and epidermal necrolysis has been observed.
Infrequent adverse effect includes- oesophageal ulceration, heart failure, hyperkalaemia, renal impairment, confusion, bronchospasm, and salt and fluid retention [11]

Photosensitivity

Like the other agents of the NSAIDs, ibuprofen has also been reported to be a photosensitising agent.[12][13] However, this only rarely occurs with ibuprofen and it is considered to be a very weak photosensitising agent when compared with other members of Non-steroidal anti-inflammatory drugs. This is because the ibuprofen molecule contains only a single phenyl moiety

and no bond conjugation, resulting in a very weak chromophore system and a very weak absorption spectrum which does not reach into the solar spectrum.

Cardiovascular risk

Ibuprofen has been reported to elevate the risk of myocardial infarction, particularly among those taking chronically high doses of ibuprofen [14]

Risk in pregnancy

Studies have found an increased risk of miscarriage with the use of ibuprofen in early pregnancy; however, there are no thorough findings in this association. There are also concerns that drugs such as ibuprofen may interfere with implantation of the early foetus, although a clear risk has not been established. When ibuprofen is used as directed in the first and second trimester of pregnancy, it is not associated with an increased risk for birth defects. However, ibuprofen is generally not used during pregnancy because there are concerns with their use during the third trimester.

Ibuprofen Overdose

Ibuprofen is the most commonly and widely used Non-steroidal anti-inflammatory agent all over the world. Since, ibuprofen was licensed as an over the counter drug, ibuprofen overdose became a common phenomenon.

The most common symptoms of ibuprofen overdose are unsteadiness, blurred vision, ringing in the ears, gastrointestinal, nausea plus vomiting, diarrhoea, stomach pain, probable loss of blood in intestinal areas or

stomach or both, headache, agitation, drowsiness, incoherence and confusion etc. Sometimes more serious symptoms are also noticed in some victims, such as seizure, gastrointestinal bleeding, metabolic acidosis, respiratory depression, hyperkalaemia, tachycardia, atrial fibrillation, coma, hepatic dysfunction, renal failure, cyanosis, and cardiac arrest etc., however these symptoms are very rare. The severity of symptoms varies with the ingested dose and the time elapsed. However, individual sensitivity also plays an important role. Generally, the symptoms observed with an overdose of ibuprofen are similar to the symptoms caused by an overdose of other NSAID’s.

Doses of ibuprofen below 100 mg/kg are less likely to produce any toxic effects. But doses of ibuprofen above 400 mg/kg are considered an overdose and can result into any of the above consequences.