# Research on

## Effect of Ibuprofen suspension On remission of fever (age≤60months)

Submitted by
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# Acknowledgements

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My Parents, Brother and Sister to whom I am greatly indebted for their blessings.

Finally, I am very grateful to my friends and relatives who encouraged me enormously.

# CERTIFICATE

This is to certify that, the thesis 'Effect of Ibuprofen on remission of fever of hospitalized children age≤60 months' submitted to the Department of Pharmacy, East West University, 43 Mohakhali C/A, Dhaka 1212, Bangladesh in partial fulfillment of the requirements for the degree of Bachelor of pharmacy (B. Pharm) was carried out by Kazi Khan-E-Alam (ID: 2005-2-70-063) under our guidance and supervision and that no part of the thesis has been submitted for any other degree. We further certify that all the sources of information and laboratory facilities availed of in this connection is duly acknowledged.

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# Abstracts

**Background:** Ibuprofen is widely used for treating fever in children. Like paracetamol, aspirin, and physical methods (such as fanning), Ibuprofen aims to provide relief from symptoms and prevent febrile convulsions. **Objectives:** To assess the effect of liquid ibuprofen for remission of fever in hospitalized children aged less than 60 months. **Materials and methods:** Twelve subjects aged less than 60 months admitted to the Institute of Child Health and Shishu Sasthya Foundation Hospital (ICH&SSF) were included in this study. The body temperature of the patients was recorded at different time interval before and after administration of liquid Ibuprofen preparation. The patients were given 10mg/kg dose of liquid Ibuprofen. Body temperature was recorded by thermometer after 15, 30, 60, 90, 120, 150 and 180 minutes of the administration of liquid Ibuprofen. **Data analysis:** Data were analyzed by using Paired sample T-test. **Result:** After administration of liquid Ibuprofen the body temperature of the patients starts to reduce from $101.92^0$F to $99.29^0$F. It takes about 3 hours to reach the lowest body temperature of $99.29^0$F. In some cases the temperature increases slightly after 1:30 to 2:00 hours of the administration of Ibuprofen, because the terminal half life of the drug is 1 to 2 hours. **Conclusion:** Liquid preparation of Ibuprofen has effect of lowering body temperature of the febrile children.

# Table of Content

# Figures

# CHAPTER-1

# Introduction

## Fever

## 1.1 Definition

A fever is usually a sign that something out of the ordinary is going in the body. For an adult, a fever may be uncomfortable, but usually isn't dangerous unless it reaches 103 F (39.4 C) or higher. For young children and infants, a slightly elevated temperature may indicate a serious infection. Fever which means a body temperature above the usual range of normal can be caused by abnormalities in the brain itself or by toxic substances that affect the temperature regulating centers (Guyton and Hall, 2003).

But the degree of fever doesn't necessarily indicate the seriousness of the underlying condition. A minor illness may cause a high fever, and a more serious illness may cause a low fever. Usually a fever goes away within a few days. A number of over-the-counter medications lower a fever, but sometimes it's better left untreated. Fever seems to play a key role in helping the body fight off a number of infections (Guyton and Hall, 2003).

Some causes of fever and also subnormal body temperatures are presented in the following figure. They include bacterial diseases, brain tumors, and environmental conditions that may terminate in heatstroke (Guyton and Hall, 2003).

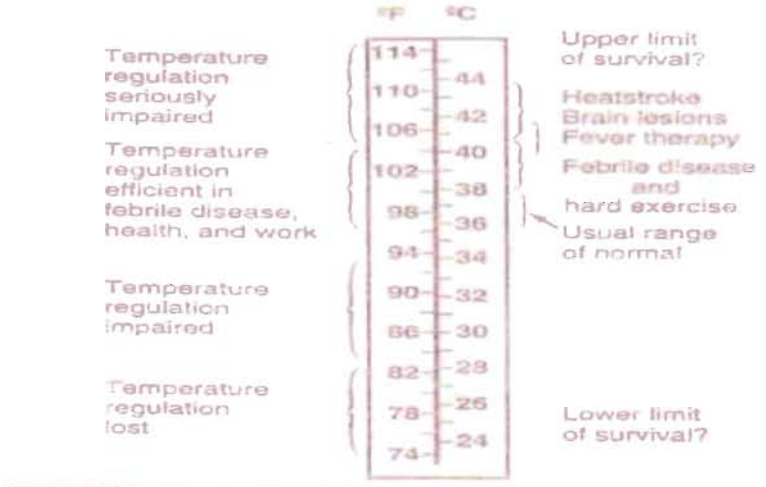



FIGURE 73-10

Body temperatures under different conditions. (Redrawn from DuBois EF: Fever. 1948. Courtesy of Charles C Thomas, Publisher, Ltd., Springfield, IL.)

Figure 1.1: Body temperature under different condition

## 1.2 Symptoms

Fever occurs when body temperature rises above its normal range. The normal average body temperature is 98 F. Fever symptoms may include:

- Sweating
- Shivering
- Headache
- Muscle aches
- Loss of appetite
- Dehydration
- General weakness

High fevers between 103 F (39.4 C) and 106 F (41.1 C) may cause:

- Hallucinations
- Confusion
- Irritability
- Convulsions

## 1.3 Generation of fever

Regulation of body temperature requires a delicate balance between the production and loss of heat; the hypothalamus regulates the set point at which body temperature is maintained. In fever this set point is elevated (Guyton and Hall, 2003).

Many proteins, breakdown products of proteins, and certain other substances, especially lipopoly saccharine toxins released from bacterial cell membranes, can cause the hypothalamic set point to rise. Substances that cause these effects are called pyrogens. It is pyrogens released from toxic bacteria or pathogens released from degenerating tissues of the body that cause fever during disease conditions due to tissue damage inflammation graft rejection, malignancy or other disease condition (Guyton and Hall,2003).

Pyrogens are of two types. Endogenous and exogenous (Guyton and Hall, 2003).

### 1.3.1Endogenous

Cytokines, especially interleukin 1, are a part of the innate immune system, are produced by phagocyte cells, and cause the increase in the thermoregulatory set-point in the hypothalamus. Other examples of endogenous pyroxenes are interleukin 6 (IL-6), and tumor necrosis factor-alpha (Guyton and Hall, 2003).

These cytokine factors are released into general circulation where they migrate to the circumventricular organs of the brain due to easier absorption caused by the blood-brain barrier's reduced filtration action there. The cytokine factors then bind with endothelial receptors on vessel walls, or interact with local microglia cells. When these cytokine factors bind, the arachidonic acid pathway is then activated (Goodman & Gillman, 2001).

### 1.3.2Exogenous

One example for the mechanism of fever caused by exogenous pyrogens includes lipopolysaccharide(LPS), which is a cell wall component of bacteria. When bacteria or breakdown products of bacteria are present in the tissue or in the blood, they are phagocytized by the blood leukocytes by, by tissue macrophage, and by large granules killer lymphocytes. All

these cells in turn digest the bacterial products and then release into the body fluids the substances interleukin 1 (IL-1), interleukin 6 (IL-6), and the tumor necrosis factor-alpha. These substances on reaching the hypothalamus, immediately activates the processes to produce fever, sometimes increases the body temperature a noticeable amount in only 8 to 10 minutes.

In other words, exogenous factors cause release of endogenous factors, which, in turn, activate the arachidonic acid pathway (Goodman & Gillman, 2001).

PGE2 release comes from the arachidonic acid pathway. This pathway (as it relates to fever), is mediated by the enzymes phospholipase A2 (PLA2), cyclooxygenase-2 (COX-2), and prostaglandin E2 syntheses. These enzymes ultimately mediate the synthesis and release of PGE2 (Goodman & Gillman, 2001).

The cytokines increases the secretion of PGE2, via increases in cyclic AMP, triggers the hypothalamus to elevate body temperature by promoting increases in heat generation and decreases heat loss (Goodman & Gillman, 2001).

## 1.4 Characteristics of febrile condition

When the set point of the hypothalamic temperature-regulating centre becomes increased to a higher level than normal, all the mechanism of rising temperature are brought into play, including heat conservation and increased heat production. Within a few hours after the set point increased to higher level, the body temperature also approaches this level, as shown in the following figure (Guyton and Hall, 2003).

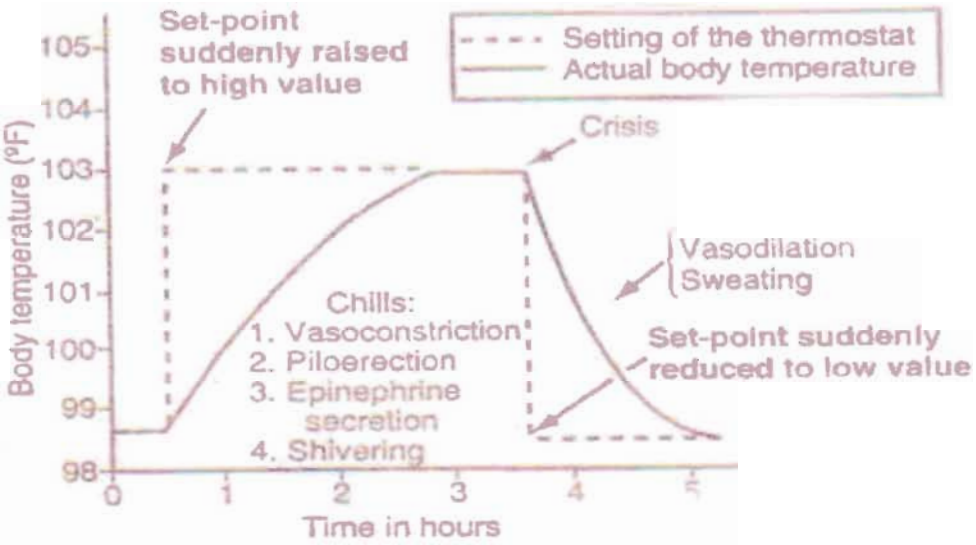



FIGURE 73–11

Effects of changing the set-point of the hypothalamic temperature controller.

Fig 1.2: Different stages of fever

### 1.4.1 Chills

When the set point of the hypothalamic temperature control centre is suddenly changed from the normal level to higher than normal, the body temperature usually takes several hours to reach the new temperature set point. Above figure shows this, demonstrating the effect of suddenly increasing the set point to a level of 103 F. Because the blood temperature is now less than the set point of the hypothalamic temperature controller, the usual responses that cause elevation of body temperature occur. During this period, the person experience chill and feels extremely cold, even though his\her body temperature may already be above normal. Also the skin becomes cold because of vasoconstriction and the person shivers. Chills can continue until the body temperature reaches the hypothalamic set point of 103 F. Then the person no longer experiences chills but instead feels nither neither cold nor hot. As long as the factor that is causing the hypothalamic temperature controller to be set this high set-point value continuous. The body temperature is regulated more or less in the normal manner-but at the high temperature set point level (Guyton and Hall, 2003).

### 1.4.2 The Crisis or Flash

If the factor that causing the high temperature is suddenly removed, the set point of the hypothalamic temperature controller is suddenly reduced to a lower value, perhaps even back to the normal level as shown in the figure. In this instance the body temperature is still 103 F, but the hypothalamus is attempting to regulate the temperature to 98.6 F. This situation is analogous to excessive heating of the anterior hypothalamic pre optic area, which causes intense sweating and development of hot skin because of vasodilatation everywhere. This sudden change of events in a febrile state as the crisis or flash (Guyton and Hall, 2003).

# CHAPTER-2

# Ibuprofen-the molecule

## 2.1Ibuprofen

Ibuprofen is the drug, that belongs to the class of Nonsteroidal Antiinflametory drugs(NSAID's). According to the chemical classification of NSAID's Ibuprofen belong to the class of Arylpropionic acid derivatives.

Considering various factors, Ibuprofen belongs to the following categories as a drug.

- Analgesics
- Analgesics, Non-Narcotic
- Anti-Inflammatory Agents, Non-Steroidal
- Anti-inflammatory Agents
- Cyclooxygenase Inhibitors
- Nonsteroidal Anti-inflammatory Agents (NSAIDs)

As a member of NSAID it plays very distinct role to remove pain and used as a drug for relief of symptoms of arthrits, primarr dismenorrhea,fever and as an analgesic, especially where there is an antiinflametory component (Goodman & Gillman,2001).

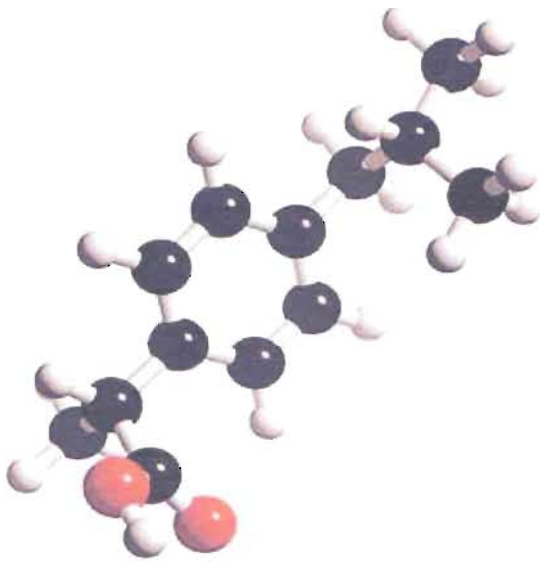


Fig 2.1: 3D structure of an Ibuprofen molecule

## 2.2 History

Ibuprofen was derived form propionic acid by researchers at the Boots Company (Boots Group Plc), UK, during the 1960s. The Boots Group is a large chain of UK pharmacies. It was discovered by Stewart Adams, with colleagues John Nicholson, Andrew RM Dunlop, Jeffery Bruce Wilson & Colin Burrows, and was patented in 1961.Dr. Adams initially tested the drug on hangover.In 1969 it was launched as a medication for the treatment of rheumatoid arthritis in the UK in 1969, and in the USA in 1974. The Boots Group was awarded the Queen's Award for Technical Achievement for the development of ibuprofen in 1987.

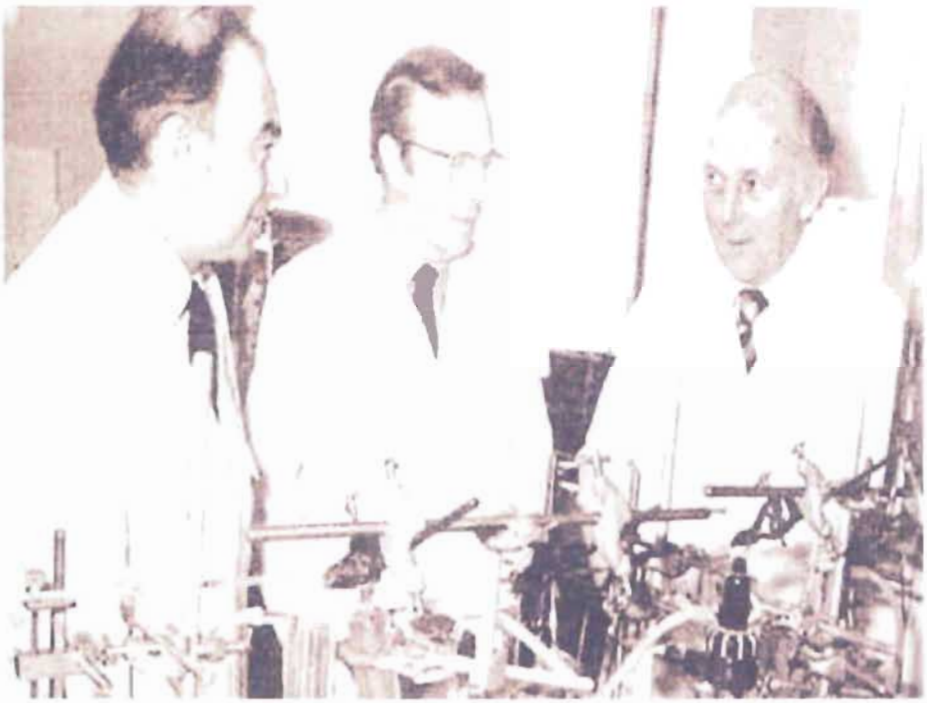


Fig 2.2: Dr Stewart Adams (right) at work with colleagues in the Boots laboratory, Nottingham

## 2.3 Chemistry

### 2.3.1 Chemical Name

α-methyl-4-(2-methylpropyl) benzeneacetic acid (Andrejus Korolkovas, 1988).

### 2.3.2 Chemical Formula

$C_{13}H_{18}O_2$

### 2.3.3 Chemical Structure



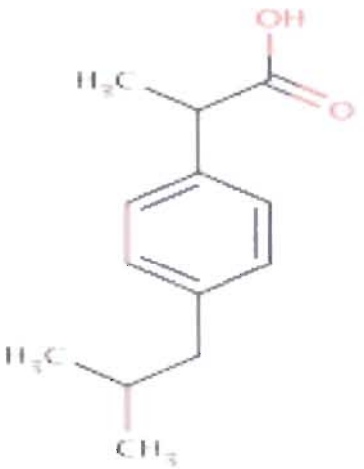
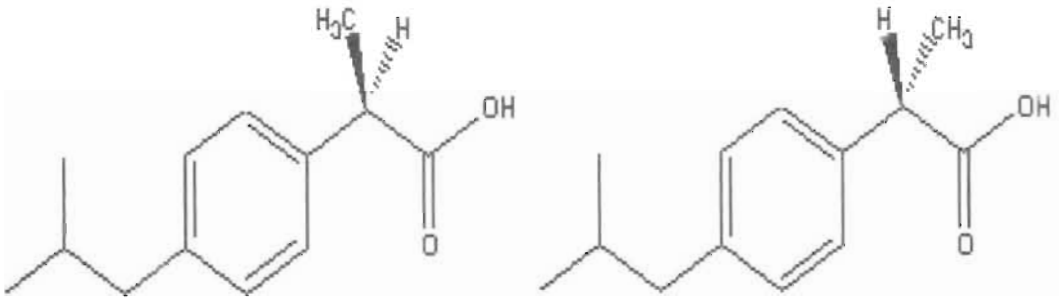



Fig2.3: Chemical structure of Ibuprofen

### 2.3.4 Stereochemistry

The molecule is composed of a carboxylic group in the right hand corner, of a phenyl group in the middle, and of an isobutyl group to the left of the image. Ibuprofen is made up of two separate molecules — R-ibuprofen and S-ibuprofen. These have the same structure but vary in their arrangement. In fact, they are isomers called enantiomers. The difference lies in how the atoms are connected in the second carbon from the right.




R - Ibuprofen S - Ibuprofen

In the R-isomer, the methyl (CH3) group is in the front. In the S-isomer, the methyl (CH3) group is in the back (JoÈrn LoÈ tsch,et..al, 2001).

Indeed it was found that (S)-(+)-ibuprofen (dexibuprofen) was the active form both in vitro and in vivo. It was logical, then, that there was the potential for improving the selectivity and potency of ibuprofen formulations by marketing ibuprofen as a single-enantiomer product (as occurs with naproxen, another NSAID). Further in vivo testing, however, revealed the existence of an isomerase (2-arylpropionyl-CoA epimerase) which converted (R)-ibuprofen to the active (S)-enantiomer. Thus, due to the expense and futility that might be involved in making a pure enantiomer, most ibuprofen formulations currently marketed are racemic mixtures (JoÈrn LoÈ tsch et.al.2001).

### 2..3.5 Synthesis of Ibuprofen

Acetylation of Isobutylbenzene(i ) with acetyl chloraid results in the 4- isobutylacetophenone; Willgerodt – Kinder reaction of ii (using sulfur and morophine) leads to the corresponding thioamide(iii) ; hidrilysis of iii gives 4-isobutylphenylacetic acid, whose ethyl ester (iv) is condensed with ethyl carbonate resulting in a malonic derivative(v) Treatment with 5 with methyl iodide in the presence of sodium ethoxide affords the intermediate (vi) which by safonifacation followed by decarboxylation leads to ibuprofen (vii) (Andrejus Korolkovas,1988).

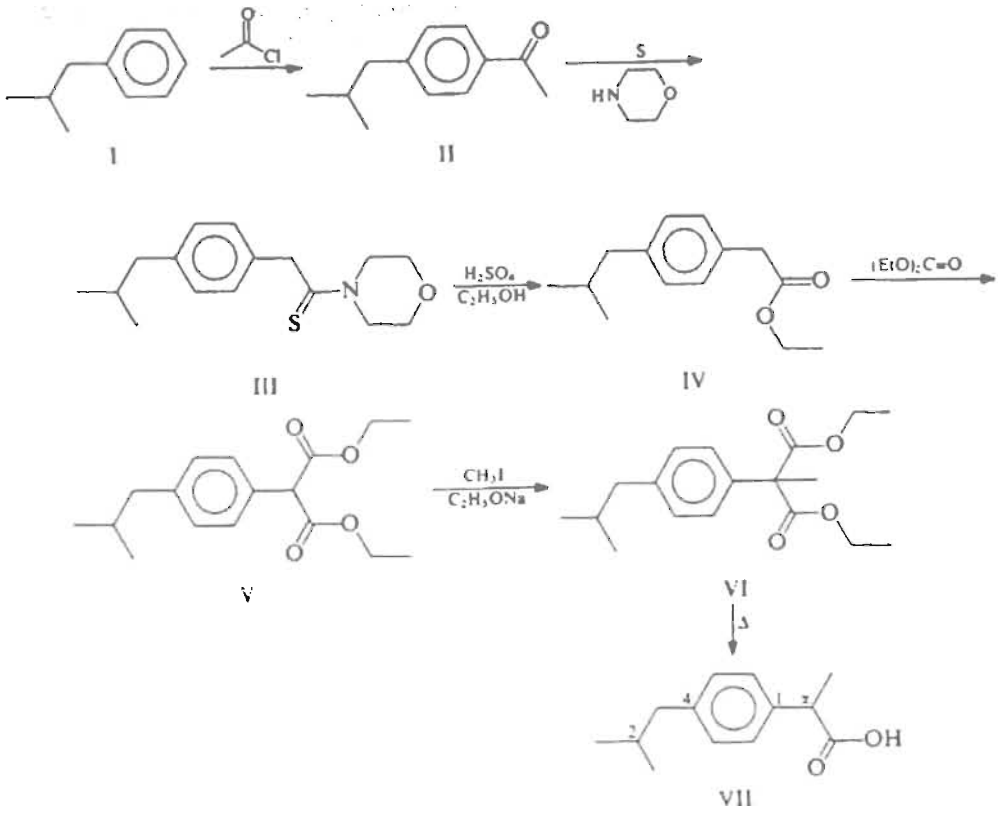



**Figure** Synthesis of ibuprofen

Fig2.4: Synthesis of Ibuprofen

## 2.4 Physical Properties

Ibuprofen is a white or almost white powder or crystals possessing a characteristics odor and a slight taste. It is practically insoluble in water: freely soluble in alcohol,chloroform, ether, and acetone, and soluble in aqueous solutions of alkali hydroxides and carbonates.The molecule has a melting point between 74°C to 77°C (Andrejus Korolkovas,1988).

## 2.5 Mechanism Action of Ibuprofen

Ibuprofen work by inhibiting the enzyme cyclooxygenase (COX), which converts arachidonic acid to prostaglandin $H_2$ ($PGH_2$).Actually Ibuprofen exibites it action by stop the synthesis of Prostaglandin (Goodman & Gillman,2001).

### 2.5.1 Prostaglandin

Prostaglandins are unsaturated carboxylic acids, consisting of of a 20 carbon skeleton that also contains a five member ring. They are biochemically synthesized from the fatty acid, arachidonic acid (KD Tripathi, 2008).

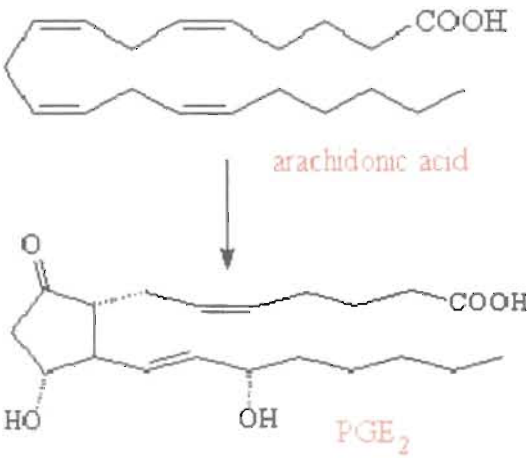



Fig 2.5: Structure of Arachidonic Acid and Prostaglandin

The prostaglandins are considered "local hormones." They have specific effects on target cells close to their site of formation. They are rapidly degraded, so they are not transported to distal sites within the body (Goodman & Gillman, 2001).

### 2.5.2 Prostaglandin Structure:

Prostaglandins are unsaturated carboxylic acids, consisting of of a 20 carbon skeleton that also contains a five member ring and are based upon the fatty acid, arachidonic acid. There are a variety of structures one, two, or three double bonds. On the five member ring there may also be double bonds, a ketone, or alcohol groups (KD Tripathi, 2008).

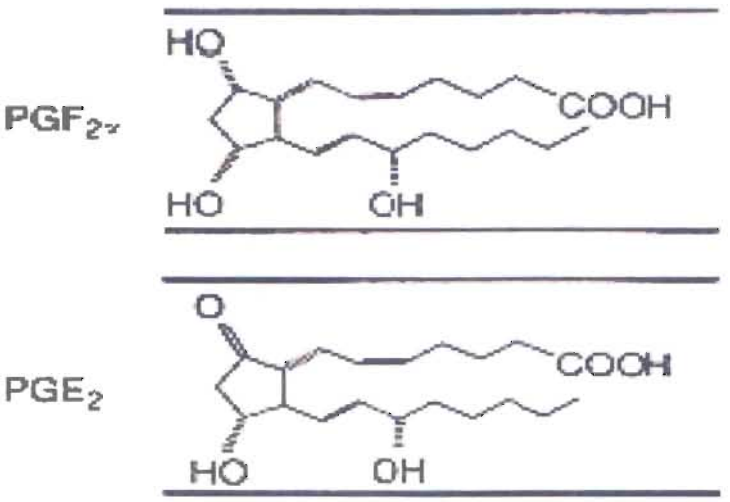



Fig2.6: structures of prostaglandins synthesized

## 2.6 Biosynthesis of Prostaglandins

Prostaglandins are produced by the oxidative metabolism of free arachidonic acid. Under normal circumstances, arachidonic acid is not available for metabolism as it is present as a conjugated component of thelipid matrix of most cellular membrane. Release of free arachidonic acid, which subsequently may be oxidatively metabolized, occurs by stimulation of phospholipase (PLA2) enzyme activity in response to some traumatic event (Wilson and Gisvold, 2004).

Through which the, the oxygenation of arachidonic acid occurs is the cyclooxygenase pathway. The cyclooxygenase pathway, so named because of the unusual bicyclic endoperoxide (PGG2) produced in the 1st step of the sequence, involves the highly stereospecific addition of two molecule of oxygen to the arachidonic acid substrate, followed by subsequent enzyme controlled rearrangements to produce an array of oxygenated prostaglandin with diverse biological activities. The 1st enzyme in this pathway, PGH synthase, is a homoprotein that catalyzes both the addition of oxygen (to from PGG2) and the subsequent reduction of the 15 position hydroperoxide to the 15-(S)- configuration alcohol (PGH2). PGH synthese, also called cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) and , have been the foicus of intensive investigation because of it's key role as the 1st enzyme of arachidonic acid cascade. These enzyme will metabolize 20-carbon fatty acids with one or more or one less double bond than arachidonic acid, leading to prostaglandins of varied degree of unsaturation (eg. PGE1 or PGE3 for which the subscript number indicates the number of double bonds in the molecule.) (Wilson and Gisvold, 2004).

Prostaglandin H2 serves as abranch point substrate for specific enzymes, leading to the production of various prostaglandins, TXA2 and PGI2 (Wilson and Gisvold, 2004). Cyclooxygenase is known to exist in two isoform COX1 and COX2 while both isoforms catalyzes the same reactions; COX1 is a constituve enzyme in most cells its activity is not changed once the cell is fully grown. On the other hand COX2 normally present in insignificant amounts but is inducible by citokinase growth factors and other stimuli during the inflammatory response. It is believed that prostaglandins produced by COX1 participate in physiological functions such as secretion mucus for protection of gastric mucosa, while those produced by COX2 lead to inflammatory and other pathological changes (KD Tripathi, 2008).

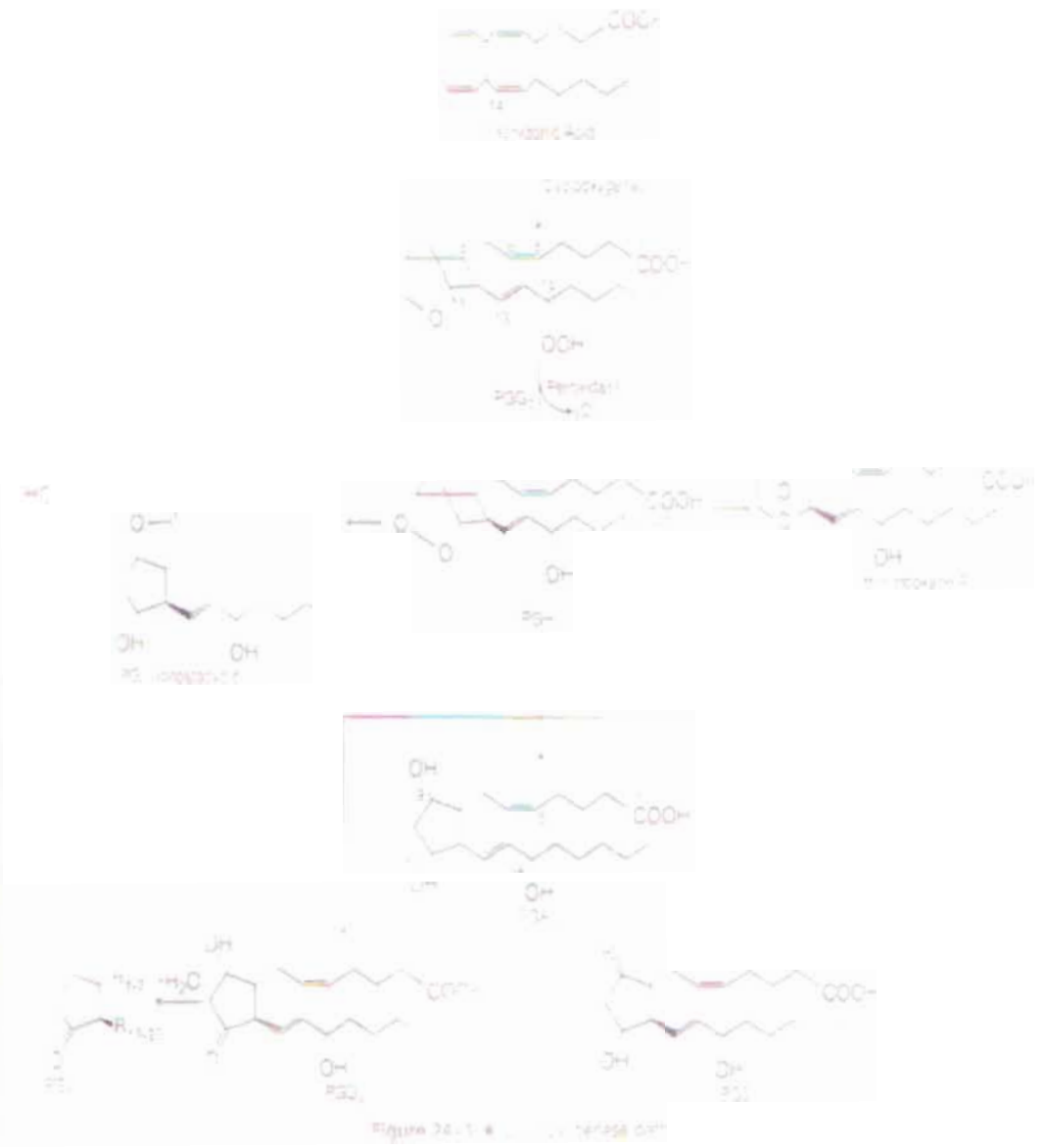


Fig2.7: Cyclooxygenase pathway of Prostaglandin synthesis from Arachidonic acid.

### 2.6.1 Functions of Prostaglandins

There are a variety of physiological effects including:

**1.** Activation of the inflammatory response, production of pain, and fever. When tissues are damaged, white blood cells flood to the site to try to minimize tissue destruction. Prostaglandins are produced as a result (KD Tripathi, 2008).

**2.** Blood clots form when a blood vessel is damaged. A type of prostaglandin called thromboxane stimulates constriction and clotting of platelets. Conversely, PGI2, is produced to have the opposite effect on the walls of blood vessels where clots should not be forming (KD Tripathi, 2008).

**3.** Certain prostaglandins are involved with the induction of labor and other reproductive processes. PGE2 causes uterine contractions and has been used to induce labor (KD Tripathi, 2008).

**4.** Prostaglandins are involved in several other organs such as the gastrointestinal tract (inhibit acid synthesis and increase secretion of protective mucus), increase blood flow in kidneys, and leukotriens promote constriction of bronchi associated with asthma (KD Tripathi, 2008).

## 2.7 Action of Ibuprofen

Ibuprofen has anti-inflammatory properties, and it belongs to a class of therapeutic agents known as nonsteroidal anti-inflammatory drugs, or NSAIDs.Ibuprofen works by inhibiting the activity of a class of enzymes called cyclooxygenases (COX). These enzymes are significant because they catalyze the synthesis of prostaglandins, molecules that have both positive and negative effects in the body. Prostaglandins are, for example, protective against the development of stomach ulcers, but they can also mediate inflammation as well as the pain response (KD Tripathi, 2008).

There is more than one COX enzyme present in our body.—definitely two, and probably at least three. It was believed that there was more than one COX enzyme, in 1991 it was discovered that there are two type of enzymes COX-1 and COX-2. It was then recognized that COX-1 is present at near constant levels in the body under all conditions (that is, it is a constitutive enzyme), whereas the levels of COX-2 could increase in response to inflammatory conditions (i.e., it is an inducible enzyme). This led to the idea that the side effects of ibuprofen, including stomach ulcers, probably arose from inhibition of the constitutive COX-1 enzyme, whereas the therapeutic benefits arose from inhibition of the inducible COX-2 enzyme. Ibuprofen binds noncovalently to a COX enzyme and thus competes with the enzyme's natural substrate (This is referred to as reversible inhibition.).

### 2.7.1 Inhibition of prostaglandin Biosynthesis by Ibuprofen

Since the principal therapeutic effects of Ibuprofen derive from its ability to inhibit prostaglandin production, the enzymatic activities involved in prostaglandin synthesis are described here briefly. The first enzyme in the prostaglandin synthesis pathway is prostaglandin endoperoxide synthase or fatty acid cyclooxygenase. This enzyme coverts arachidonic acid to the unstable intermediates PGG2 and PGH2. It is now appreciated that there are two forms of cyclooxygenase, termed cyclooxygenase-I (COX-1) and cyclooxygenase-2 ( COX-2). COX 1 is a constitutive isoform found in most normal sales and tissues, while COX-2 is induced in settings of inflammation by cytokines and inflammatory mediators. How ever COX-2 also is constitutively expressed in certain areas of kidney and brain. Importantly, COX-1, but not COX-2, is constitutively expressed in the stomach .This accounts for the markedly reduced occurrence

of gastric toxicity with the use of selective inhibitors of COX-2.The fate of PGG2 or PGH2 cyclooxigenase products differs from tissue to tissue, depending on the particular PGG2 or PGH2 metabolizing enzymatic activities present. Arachidonic acid also can be converted via the 5 – lipoxygenase pathway, to a verity of leukotrienes. Ibuprofen inhabit the cyclooxigenase enzyme and prostaglandin production, they do not inhibit lipoxygenase pathways and, hence, donot suppress leukotriene formation (Goodman & Gillman, 2001).

## 2.8Beneficial actions due to PG Synthesis inhibition

- Analgesia; Prevention of pain nerve ending sensitization
- Antipyresis
- Anti-inflammatory
- Antithrombotic
- Closure of Ductus Aertosus

### Analgesia:

PGs induce hyperalgesia by affecting the transducing property of free nerve ending- simuli that normally donot elicit pain is able to do so. Ibuprofen do not affect the tenderness induced by direct application of PGs, but bloc the pain sensitizing application of PGs, but block the pain sensitizing mechanism induced by bradykinin, THFa , interleukins and other algesic substances, therefore more effective against inflammation associated pain (KD Tripathi,2008).

### Antipyresis:

NSAIDs reduce body temperature in fever, but don't cause hypothermia in normothermic individuals. Fever during infection is produced through the generation of pyrogen, ILs, TNFa, interferons which include PG production in hypothalamus-raise its temperature set point. Ibuprofen block the action of pyrogens but not that of PGE2 injected into hypothalamus. The isoform present at this site appears to be COX-2. However, Fever can occur through non-PG mediated mechanisms also; inhibition of COX does not entirely explain the antipyretic action of Ibuprofen (KD Tripathi, 2008).

### Anti-inflammatory:

The most important mechanism of Anti-inflammatory action of Ibuprofen is considered to be inhibition of PG synthesis at the site of injury. The Anti-inflammatory potency of ibuprofen corresponds with its potency to inhibit COX. PGs are only one of the mediators of inflammation; inhibition of COX does not depress the production of other mediator like LTs, PAF, cytokines etc (KD Tripathi, 2008).

### Antiplatelet Aggregatory:

Ibuprofen inhibit synthesis of both proaggregatory (TXA2) and antiaggregatory(PGI2) prostaniods, but effect on platelet TXA2 predominates ---therapeutic doses of most Ibuprofen inhibit platelet aggregation: bleeding time is prolonged (KD Tripathi,2008).

### Ductus Arteriosus Closure:

During foetal circulation ductus arteriosus is kept patent by local elaboration of PGE2 and PGI2. Administration of Ibuprofen in late pregnancy has been found to promote premature closure of ductus in some cases (KD Tripathi, 2008).

## 2.9 Dose of Ibuprofen

Low doses of ibuprofen, 200 mg, and sometimes 400, mg are available over the counter (OTC) in most countries. Ibuprofen has a dose-dependent duration of action of approximately 4–8 hours, which is longer than suggested by its short half-life. The recommended dose varies with body mass and indication. Generally, the oral dose is 200–400 mg (5–10 mg/kg in children) every 4–6 hours, adding up to a usual daily dose of 800–1200 mg. 1200 mg is considered the maximum daily dose for over-the-counter use, though under medical direction, a maximum daily dose of 3200 mg may sometimes be used in increments of 600–800 mg (KD Tripathi,2008).

For antipyretic action, daily doses of 1200 mg for adults and 800 mg for children, in divided portions may be given.For rheumatoid arthritis and ostearthritis, daily doses of up to 3200mg in divided portions may be given, although the usual dose is 1200 to 1800 mg. In juvenile rheumatoid arthritis up to 40 mg/kg of body weight daily in divided doses may be given. It also may be possible to reduce the dasase for maintenanace purpose. For mild to moderate pain, especially that of primary dismenorrhoea, the usual dosage is 400 mg every 4 to 6 hours as needed (Goodman & Gillman, 2001).

A dosage chart of Ibuprofen is given as follows:

| **Age*** | **Weight†** | **Drops 40 mg/1.5 ml** | **Elixir 100 mg/5 ml** | **Chewable Tablets 50 mg tabs** |
|---|---|---|---|---|
| 6-11 months | 12 - 17 lbs (5.5 - 7.7 kg) | 1 dropper | --- | --- |
| 1-2 years | 18 - 23 lbs (8.2 - 10.5 kg) | 1 1/2 droppers | --- | --- |
| 2-3 years | 24 - 35 lbs (10.9 - 15.9 kg) | 2 droppers | 1 tsp | --- |
| 4-5 years | 36 - 47 lbs (16.3 - 21.4 kg) | --- | 1 1/2 tsp | 3 tabs |

**Table**: 1 Dosage chart of Ibuprofen.

*Note: Age is provided as a convenience only. Dosing for fever should be based on baseline weight.

Weight given is representative of the age range.

## 2.10 Pharmacokinetic features of Ibuprofen

Ibuprofen is a racemic mixture of [-]R-and [+]S-isomers. *In vivo* and *in vitro* studies indicate that the [+]S-isomer is responsible for clinical activity. The [-]R-form, while thought to be pharmacologically inactive, is slowly and incompletely (~60%) interconvert into the active [+]S species in adults. The degree of interconversion in children is unknown, but is thought to be similar. The [-]R-isomer serves as a circulating reservoir to maintain levels of active drug. Ibuprofen is well absorbed orally, with less than 1% being excreted in the urine unchanged. It has a biphasic elimination time curve with a plasma half-life of approximately 2 hours. Studies in febrile children have established the dose-proportionality of 5 and 10 mg/kg doses of ibuprofen. Studies in adults have established the dose-proportionality of ibuprofen as a single oral dose from 50 to 600 mg for total drug and up to 1200 mg for free drug (G. Katzung, 2001).

### 2.10.1 Absorption

Ibuprofen is rapidly absorbed after oral administration and peak concentration in plasma are observed after 15 to 30 minutes. The half life in plasma is about 2 hours (Goodman & Gillman, 2001).

When Ibuprofen is taken with Antacid containing magnesium hydroxide the absorption is not hampered. Also administration of Ibuprofen with Ranitidine or Cemetidine does not affect the absorption of Ibuprofen (Pertti J. Neuvenen, 1990).

Single doses of Magnesium hydroxide (850mg) increased the area under the plasma ibuprofen concentration-time curve between 0 and 1 h by 65% ($P < 0.05$) and the peak concentration of ibuprofen in plasma by 31% ($P < 0.01$). The time to peak was shortened by about 0.5 h (Pertti J. Neuvenen, 1990).

When rapid onset of the analgesic effect of ibuprofen is required, concomitant

Ingestion of an antacid, which contains magnesium hydroxide without aluminium, is

recommended (Pertti J. Neuvenen, 1990).

### 2.10.2 Distribution

Ibuprofen, like most drugs of its class, is highly protein bound (>99% bound at 20 mcg/mL). Protein binding is saturable and at concentrations >20 mcg/mL binding is non-linear. Based on oral dosing data there is an age- or fever-related change in volume of distribution for ibuprofen. Febrile children <11 years old have a volume of approximately 0.2 L/kg while adults have a volume of approximately 0.12 L/kg. The clinical significance of these findings is unknown. Ibuprofen is extensively bound in plasm protien, but the drug occupies only a fraction of the total drug binding sites at usual concentrations. Ibuprofen passes slowly into the synovial spacesand may remain there in higher concentration as the concentration in plasma declain (Goodman & Gillman, 2001).

### 2.10.3 Metabolism

Metabolism occurs via hepatic bio transformetion. Metabolism involve Cytochrome P450 2C9 (CYP2C9) and Monoamine oxidase type B (MAO-B) enzymes (S.M. Sanins et.al..1990)

Ibuprofen is administered as recemic mixture. After administration the R-form is converted into S-form in liver by following pathway.

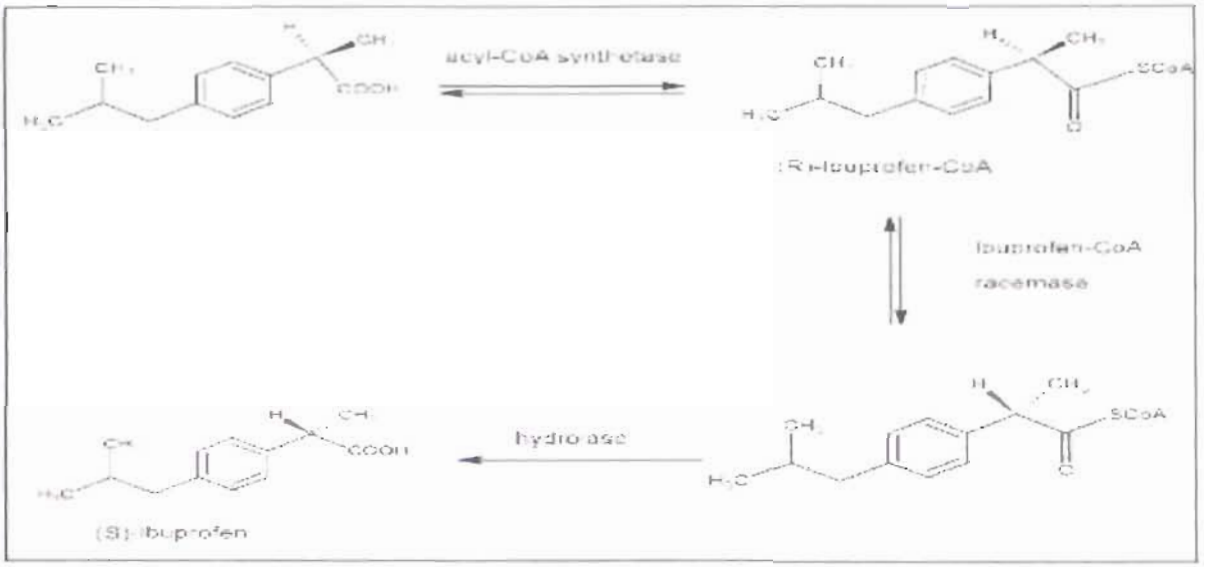



**Figure 2:** Mechanism of metabolic inversion of ibuprofen

Figure 2.8: Metabolic Inversion of Ibuprofen

Hydroxylation of the isobutyl side chain at the sub terminal carbon (to give hydroxyibuprofen) proved to be the major route of metabolism of both R(-)-ibuprofen and S(+)-ibuprofen, while formation of the corresponding diastereoisomeric 2-methylpropionic acid derivatives (carboxyibuprofen) was of minor quantitative importance Enzymes which plays key role in the metabolism of ibuprofen include CYP268,and CYP269 (S.M. Sanins et.al.1990)

### 2.10.4Elimination

Ibuprofen is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose. It has a biphasic plasma elimination time curve with a half-life of approximately 2.0 hours. There is no difference in the observed terminal elimination rate or half-life between children and adults; however, there is an age- or fever-related change in total clearance. The excretion of ibuprofen is rapid and complete. More than 90% of an ingested dose is excreted in the urine as metabolites of their conjugates. The major metabolites are a hydroxylated and a carboxylated compound (Goodman & Gillman, 2001).

## 2.11 Uses of Ibuprofen

- Ibuprofen is used as a simple analgesic and antipyretic. It is particularly effective in dysmenorrheal in which the action is clearly due to PG synthesis inhibition. It is available as an OTC drug (KD Tripathi, 2008).
- Ibuprofen is widely used in rheumatoid arthritis, osteoarthritis and other musculoskeletal disorders, especially where pain is more prominent than inflammation (KD Tripathi, 2008).
- Ibuprofen is indicated in soft tissue injuries, fractures, vasectomy, tooth extraction, postpartum and post operatively: suppress swelling and inflammation (KD Tripathi, 2008).

## 2.12 Side effects

Following side effects have observed due to the administration of Ibuprofen.

- Gastrointestinal side effects experienced by 5% to 15% of patients taking ibuprofen. Common gastro intestinal side effects include: epigastria pain, nausea, heart burn, and sensation f fullness in gastrointestinal drug (Goodman & Gillman, 2001).
- Thrombocyptopenia
- Skin rashes
- Headache
- Dizziness
- Blurred vision
- Toxic amblyopia
- Fluid retention
- Edema
- Chest pain, weakness, shortness of breath, slurred speech, problems with vision or balance and aiso skin itching or rash is observed (KD Tripathi, 2008).

## 2.13 Side Effects by Body System

### 2.13.1Gastrointestinal

Inhibition of PGE2, which suppress gastric acid secretion, helps maintain mucosal barrier and acid secretion, helps maintain mucosal barrier and regulatory microcirculation. This inhibition results Erosive gastritis and peptic ulceration (Charles R. Craig and Robert E. Stitgel, 1997).

### 2.13.2 Anti-platelet

Inhibition of synthesis of thromboxane A2 by platelets that results prolonged bleeding time and GI bold loss (Charles R. Craig and Robert E. Stitgel, 1997 ).

### 2.13.3 Renal

Inhibition of synthesis of renal PG involved in regulation of renal bold flow, glomerular filtration and renal sodium and water excretion also involved in mediation of rennin release. That results fluid retention, diminished sodium excretion, pretrial a jotemia (Charles R. Craig and Robert E. Stitgel, 1997).

### 2.13.4 Allergic

Inhibition of cyclo-oxygenase pathway, allowing lypo-oxygenase pathway to dominate in suseeptible individual. That results broncho-spasm, urticaric, rhinitis, muscel polyposis (Charles R. Craig and Robert E. Stitgel, 1997).

### 2.13.5 Uterine

Loss of contractile effects of PGs on uterine muscles. That results delayed parfurition dystocia (Charles R. Craig and Robert E. Stitgel, 1997).

## 2.14 Contraindications with other diseases

Ibuprofen can increase the risk of life-threatening heart or circulation problems, including heart attack or stroke. Ibuprofen is not recommended for use just before or after having heart bypass surgery.

Ibuprofen also increases the risk of serious effects on the stomach or intestines, including bleeding or perforation. Older adults may have an even greater risk of these serious gastrointestinal side effects.

Ibuprofen is not recommended for use if any one is allergic to ibuprofen, aspirin or other NSAIDs.

The contraindications include:

- A history of heart attack, stroke, or blood clot
- Heart disease, congestive heart failure, high blood pressure
- A history of stomach ulcers or bleeding
- Asthma
- Polyps in your nose
- Liver or kidney disease
- Systemic lupus erythematosus (SLE)
- A bleeding or blood clotting disorder

(Charles R. Craig and Robert E. Stitgel, 1997).

## 2.15 Contraindications with Drugs

**Antihypertensive Drugs:** These are drugs taken for hypertension. In some cases Ibuprofen increases the blood pressure in those patients who are taking antihypertensive (KD Tripathi, 2008).

**Anti-inflammatory painkillers:** Patients who are taking diclofenac, indometacin, or naproxen are should not prescribe to take ibuprofen because of the increased risk of stomach bleeding (KD Tripathi, 2008).

**Aspirin:** Ibuprofen taken in combination with aspirin significantly raises the risk of stomach bleeding. Patients taking low-dose aspirin for blood thinning should not take ibuprofen, because the blood thinning effect will be diminished (KD Tripathi, 2008).

**Lithium:** A medication sometimes prescribed for certain mental disorder and illnesses. Ibuprofen can make it harder for the body to eliminate lithium, resulting in high and potentially dangerous levels of lithium in the body (KD Tripathi, 2008).

**Methotrexate:** Used in the treatment of cancer and some auto-immune diseases. Ibuprofen can make it harder for the body to eliminate methotrexate, resulting in high and potentially dangerous levels of methotrexate in the body (KD Tripathi, 2008).

**Tacrolimus:** This drug is mainly used with patients who have received an organ transplant so that the body's immune system does not reject the new organ. Ibuprofen with tacrolimus can cause kidney damage (KD Tripathi, 2008).

**SSRI (selective serotonin reuptake inhibitors) antidepressants:** Drugs, such as citalopram, fluoxetine, paroxetine and sertraline, taken with ibuprofen can increase the risk of bleeding.

**Warfarin:** This is an anticoagulant drug (a blood thinner); it stops the blood from clotting. Ibuprofen taken with warferin can reduce the drug's anticoagulant effects (KD Tripathi, 2008).

## 2.16 Dosage forms of Ibuprofen

| Form | Route |
|---|---|
| **Capsule** | **Oral** |
| **Suspension** | **Oral** |
| **Tablet** | **Oral** |
| **Tablet, chewable** | **Oral** |

**Table: 2** Different dosage forms of Ibuprofen and their route of administration


# CHAPTER-3

## 3.1 Hypothesis

After administration of liquid preparation of Ibuprofen, the body temperature of children ≤60months will be reduced.

## 3.2 Aim of the Study

Fever is a frequent medical sign that describes an increase in internal body temperature to levels above normal.

The present study was designed to assess:

- To find the effect of the liquid preparation of Ibuprofen for remission of fever in hospitalized children age ≤ 60 months.
- Whether the Ibuprofen liquid preparations have any effect on the febrile patient or not.

## 3.3 Significance of the study

Fever is a frequent medical sign that describes an increase in internal body temperature to levels above normal. Fever is most accurately characterized as a temporary elevation in the body's thermoregulatory set-point, usually by about 1–2 °C. Fever differs from hyperthermia.

A fever isn't an illness itself, but it's usually a sign that something out of the ordinary is going on in your body. Fevers aren't necessarily bad. In fact, fevers seem to play a key role in helping the body fight off a number of infections.

A fever may be uncomfortable, but it usually isn't dangerous unless it measures 103° F or higher. For very young children and infants, however, even slightly elevated temperatures may indicate a serious infection.

Ibuprofen has a mild beneficial effect on the symptoms of viral illness in childhood. However, the child may still remain unwell.

Liquid preparation of Ibuprofen is effective in reducing fever in hospitalized young Children (aged ≤60 months)

# CHAPTER-4

# Materials and Methods

## 4.1 Research Design

16 patients with Fever were enrolled in the study age ≤10year.

## 4.2 Sample characteristics and data collection

The sample was collected from the Institute of Child Health and Shishu Sasthya Foundation Hospital (ICH&SSF), Mirpur-2; Dhaka. Number of outdoor patients with fever every day are about 200, and number of indoor patient every day are about 6-10 (approximate). Fifty three subjects meeting the following inclusion and exclusion criteria were sampled.

### Inclusion criteria

- Patient : Fever
- Age : Above 1 month
- Sex: Both male and female

### Exclusion Criteria

Children with additional clinical complications other than fever will be excluded from the study.

- Very sick
- Convulsive patient
- Heart failure
- Needing $O_2$
- Diarrhea
- Constipation

Administration of Ibuprofen liquid preparations to febrile patients and case histories were collected only with consent from the patients or their respective attendants.

After administration of Ibuprofen liquid preparation body temperature of patients measured by digital thermometer each interval, the temperature recorded to the paper and case histories of the respective patients were recorded. Each record was cross-referenced in the notebook with the corresponding patient data.

## 4.3 Statistical Analysis

Data were analyzed using SPSS for widows version 12 (SPSS, Inc., Chicago,IL). All the data of the study sample was entered from each patient's history sheet. Descriptive statistics were done for major variables of interest, including the population, age distribution and different temperature of different time interval using Paired sample T-test. A probability level of 0.05 was considered statistically significant.

## 4.4 Study Period

Study period untill the patient was treated in the hospital before discharging.

## 4.5 Patients personal information

- Name
- Age
- Sex
- Weight
- Address
- Contact number

## 4.6 Operation of the Thermometer

Digital thermometer is used for the determination of the body temperature. Digital Thermometer is a durable and precise medical device. Here are some helpful hints to help you get the best performance from the product.

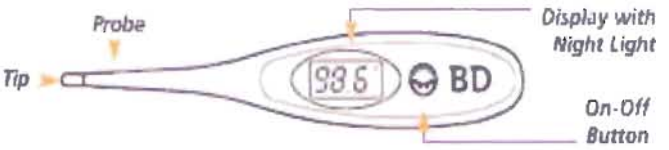



Fig11: Digital thermometer

Press button to turn on the thermometer a beep signal will sound and, just for a second, the display will read as follows:

This is a "function check" and it means the thermometer is working properly. The thermometer remembers the last temperature it took. It will automatically show this last temperature after the 1 second function check. If this is the first time you are using the thermometer (or if the thermometer did not record any temperature the last time it was turned on) for a 3 second period it will display:

After both the 1 second function check and the 3 second display of the last temperature, the display will start flashing. This flashing degrees °F indicates the thermometer is ready to take a temperature.

Temperature can be taken oral, underarm (auxiliary) or rectal method.

Underarm (Auxiliary) Method: This method for babies or very young children. Although simpler, the auxiliary method is less accurate and takes longer.

Make sure the underarm is dry and there is no material between the chest and arm. Point the thermometer upward and place the tip well into the patient's underarm. Fold patient's arm over chest to hold the thermometer in place and keep air away from the underarm.

Normally, the steady beep will continue for about one minute and then you will hear the three rapid "completion" beeps. These three rapid beeps confirm that the temperature measurement is complete. At this time the degrees °F sign will also stop flashing. In auxiliary use, ignore the completion beeps and leave thermometer in place for a full four minutes.

After hearing the three rapid beeps that signal completion, remove thermometer from mouth and read temperature on display; temperature reading will not change while the power remains on.

# Chapter 5

# Results

## 5.1:%Distribution of male and female patients under study (n=16)

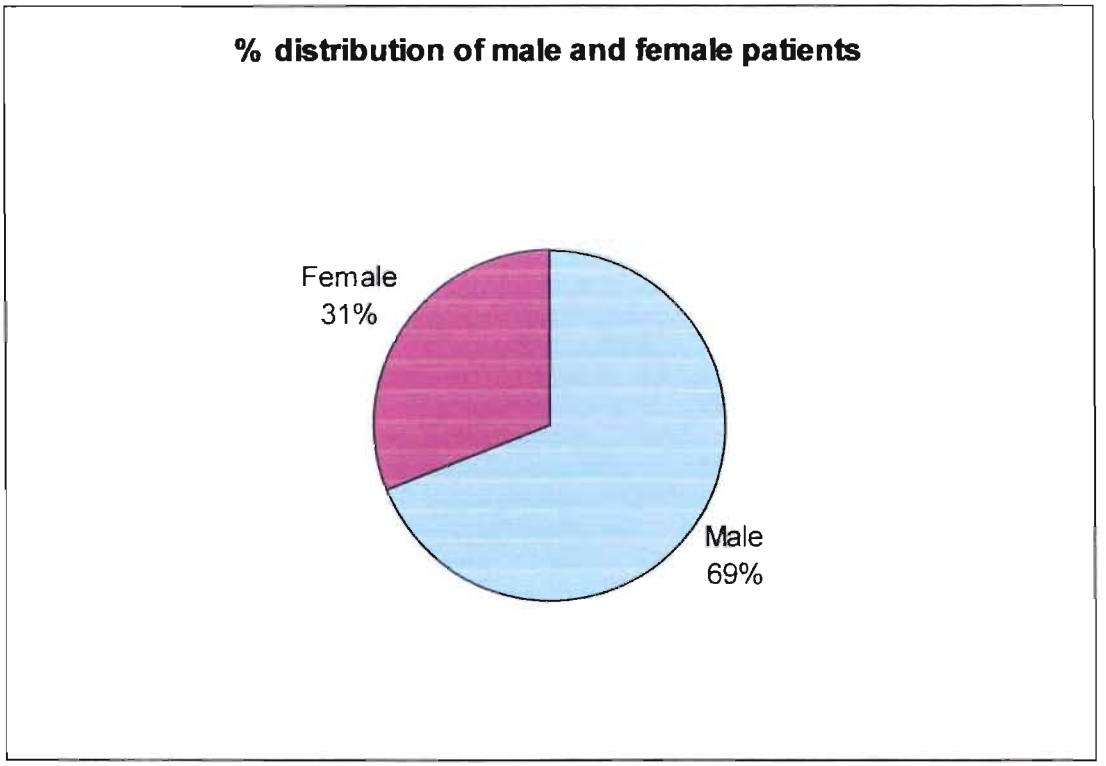



Fig 5.1 : % Distribution of male and female patients

Clinical trial of Ibuprofen suspension was performed with 16 patients (n=16). Where no of male patients were 11(68.75%) and no f female patients were 5 (31.25%). Figure 5.1 representing the percent distribution of male and female patients.

## 5.2: Number of the patients with fever according to the sex and different age groups (n=16)

| Sex | 0 to 12 month | 13to 24 month | 25 to36 month | 37 to48 month | 49 to60 month | 61 to72 month | 73 to84 month | 85 to96 month | Above 96 months |
|---|---|---|---|---|---|---|---|---|---|
| Male (n=11) | 1 | 6 | 1 | 0 | 1 | 1 | 1 | 0 | 0 |
| Female (n=5) (n=3) | 1 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |

Figure 5.2: Number of the fever patients according to the sex and different age groups.

## 5.3The age of male and female patients with fever (n=16)

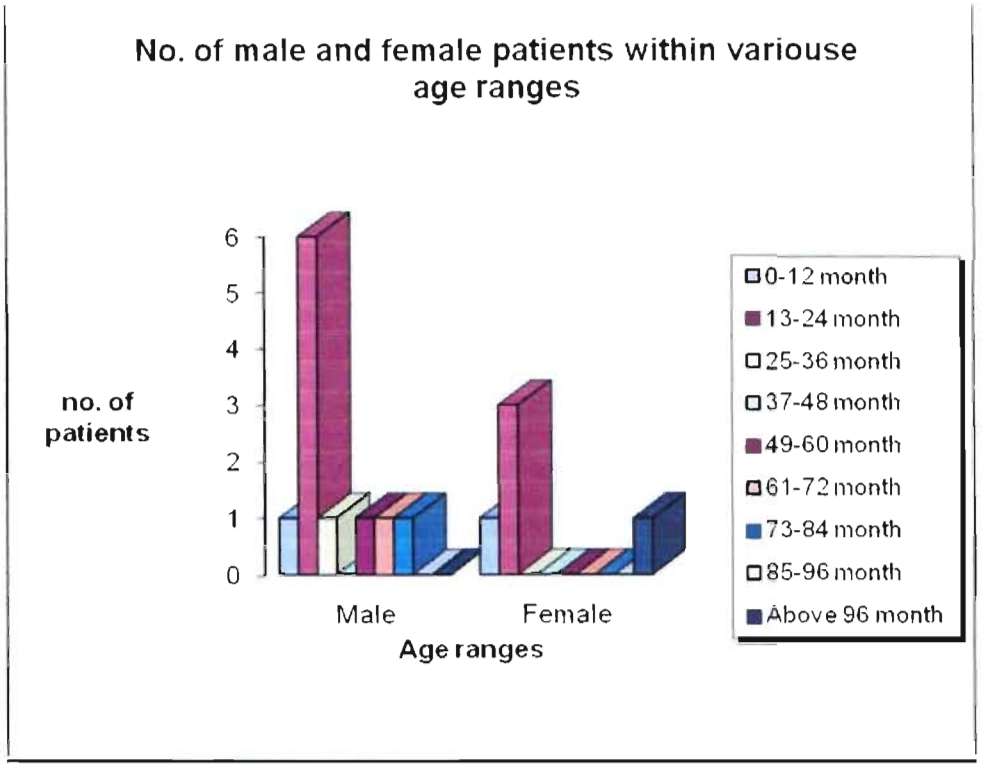



Figure 5.3 : No of Male and Female within various Age Ranges

Above graph represents the number of male and female patients within various age ranges.

## 5.4 Effect of Ibuprofen on Febrile patients

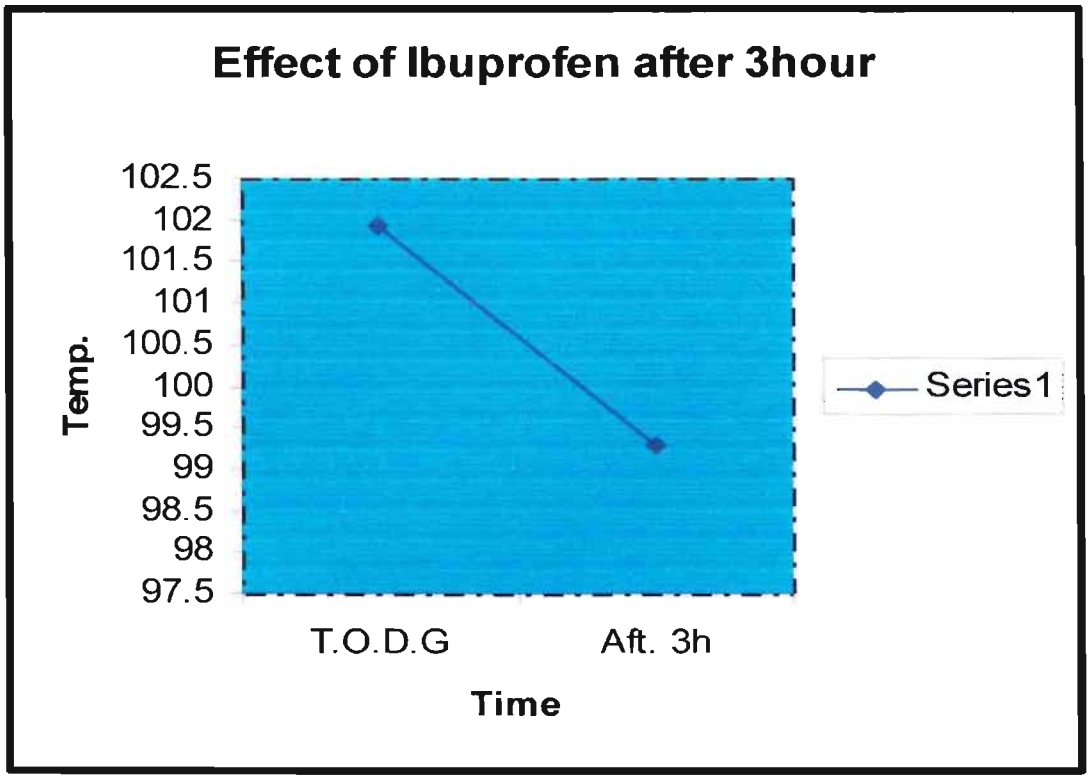



Fig 5.4: Effect of Ibuprofen on Febrile patients

Figure 5.4 actually representing the reduction of temperature of the febrile patients after 3 hours of the administration of Ibuprofen. The mean temperature calculated at the time of drug given was 101.92° F and at the end of the study it was 99.29° F.

## 5.5 Comparison of the effect of Ibuprofen on male and female febrile patients (n=16)

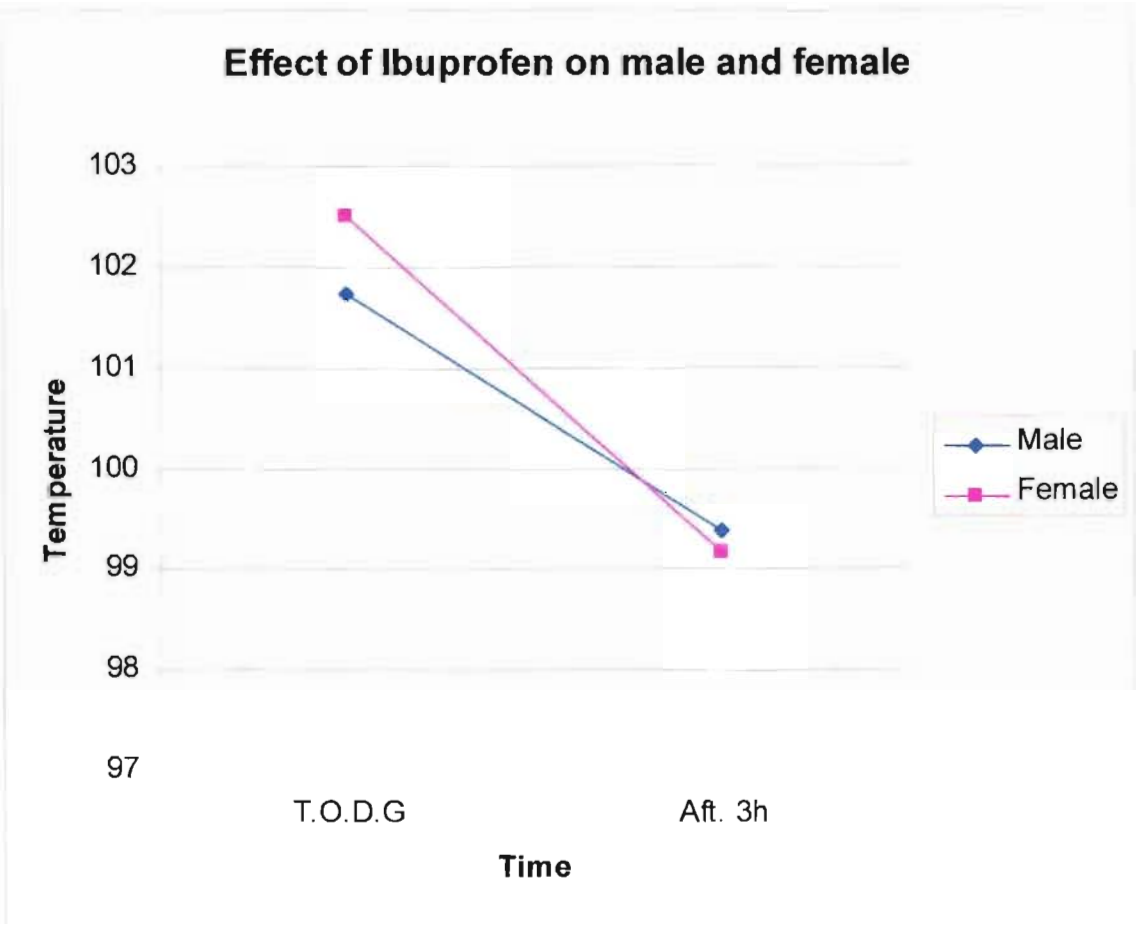



Fig 5.5: Comparison of the effect of Ibuprofen on male and female febrile patients

Figure 5.5 shows that, a comparative study of the effect of Ibuprofen on male and female patients is represented. At the time of drug given the mean temperature of male was 101.75° F and the mean temperature after 3 hours was 99.37° F. In case of female the mean temperature at the time of drug given was 102.50° F and after 3 hours it was 99.16° F.

## 5.6 Mean age of male and female patients with fever

| Sex | Mean Age (month) ± SD |
|---|---|
| Male (n=11) | 33.54±26.10 |
| Female (n=5) | 53.60±36.10 |

Table 5.6: The mean age (months) of male and female patients with fever

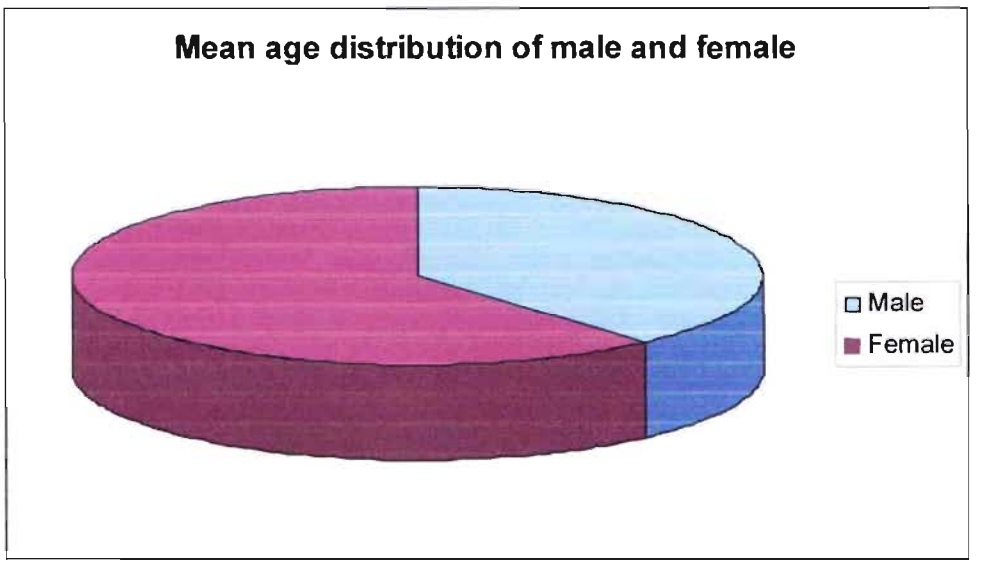



Fig 5.6: Mean age distribution of male and female

Figure 5.6 is representing the mean age of male patients is 33.54±26.10 and the female patients is 53.60±36.10.

## 5.7 Mean temperature of the patients with fever at different time intervals (n=16)

Table 19 shows the mean body temperature of the patients with fever at different time intervals.

| Time | Mean temperature ± SD (°F) |
|---|---|
| Before drug administered | 101.92 |
| After 15 minutes | 101.71± .98* |
| After 30 minutes | 100.97 ± 1.14* |
| After 1 hour | 99.94 ±1.07 * |
| After 1.5 hour s | 99.48±1.53 * |
| After 2 hours | 99.68 ±2.06 * |
| After 2.5 hours | 99.00±1.5 * |
| After 3 hours | 99.29± 1.61* |

***p*=0.000; comparison is done between before and after administering the liquid Ibuprofen.**

Table 5.7: The mean body temperature of the patients with fever at different time intervals.

## 5.8 Body temperature of the patients with fever at different time intervals (n=16)

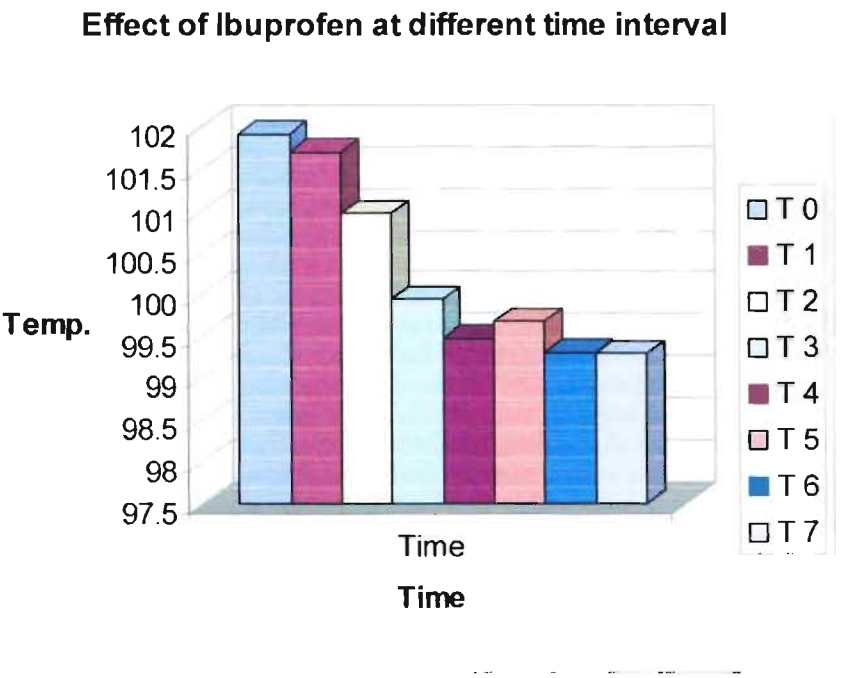



Fig 5.8: Effect Ibuprofen at different time interval

Figure 5.8 shows the body temperature of the patients at different time intervals. The body temperature of the patient was 101.92$^0$F before administration of the liquid Ibuprofen (T0). After administration of liquid Ibuprofen the body temperature was 101.71$^0$F after 15 minutes(T1), 100.97$^0$F after 30 minutes(T2), 99.94$^0$F after 60 minutes(T3), 99.48$^0$F after 90 minutes(T4), 99.68$^0$F after 120 minutes(T5), 99$^0$F after 150 minutes(T6) and 99.29$^0$F after 3 hours(T7).

Here,

## 5.9 : Mean age (months) of male and female patients with fever, aged ≤60 month (n=12).

The mean age of the female is 13.33 ±2.51 and male is 23.66 ±15.46 (Table

| Sex | Mean Age (month) ± SD |
|---|---|
| Male (n=9) | 23.66 ±15.46 |
| Female (n=3) | 13.33 ±2.51 |

Table 5.9: The mean age (months) of male and female patients' aged ≤1year with fever.

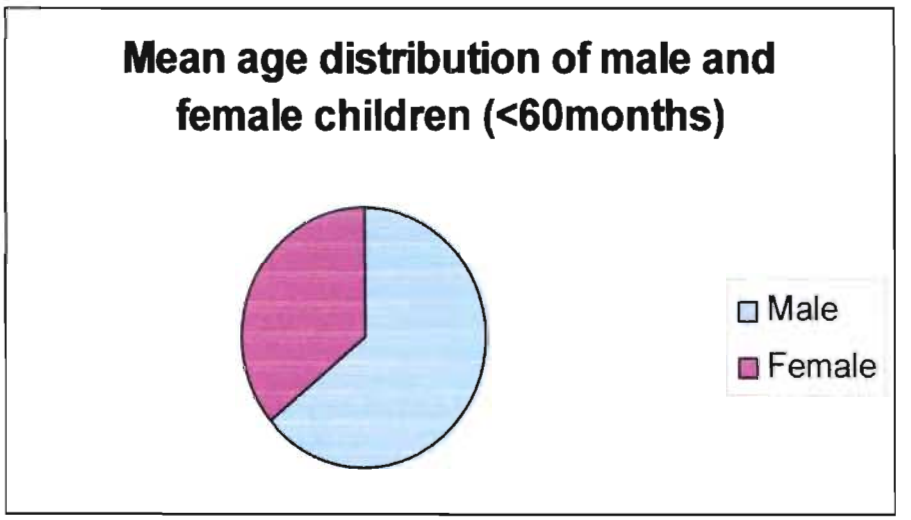



Fig: 5.9: Mean age distribution of male and female patients

## 5.10 Body temperature of the patients at different time intervals (n=12).

Table 5.10 shows the mean body temperature of the patients with fever at different time intervals.

| Time | Mean temperature ± SD (°F) |
|---|---|
| Before drug administered | 102.00 |
| After 15 minutes | 101.95± 0.93* |
| After 30 minutes | 101.20± 0.95* |
| After 1 hour | 100.14± 0.93* |
| After 1.5 hour s | 99.60± 1.35* |
| After 2 hours | 99.79± 2.11* |
| After 2.5 hours | 99.35± 1.2* |
| After 3 hours | 99.25± 1.2* |

***p*=0.000; comparison is done between before and after administering the liquid Ibuprofen.**

Table 5.10: Body temperature of the patients at different time intervals.

## 5.11: Body temperature of the patients' aged ≤ 60 months at different time intervals (n=12)

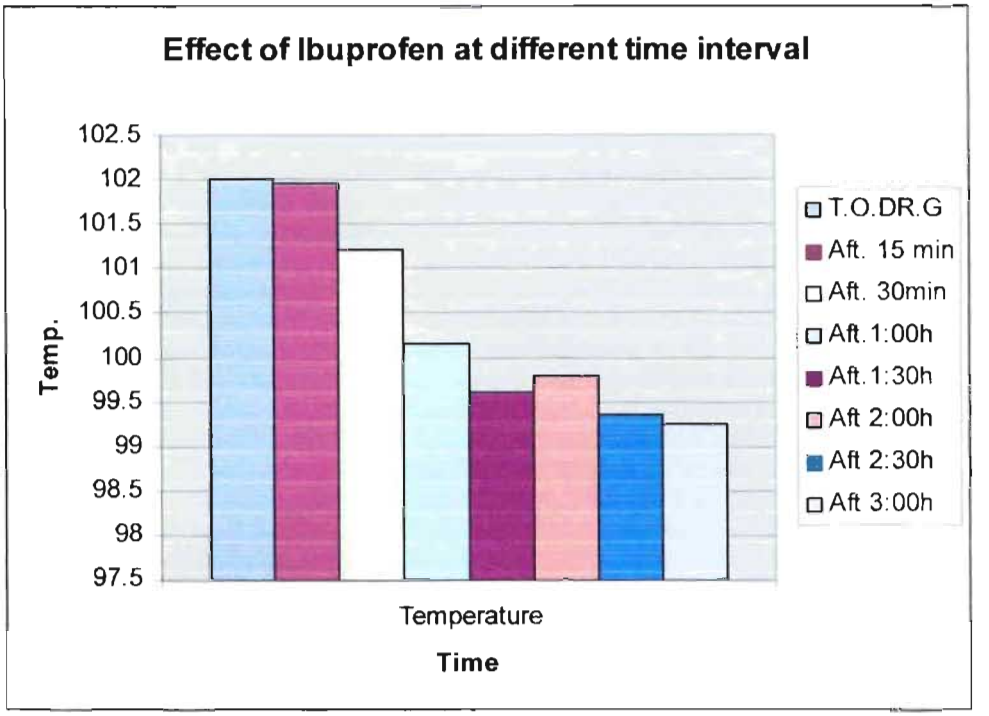



Fig 5.11: Effect of Ibuprofen

Figure 5.11 shows the body temperature of the patients at different time intervals. The body temperature of the patient was 102.00$^0$F before administration of the liquid Ibuprofen (T0). After administration of liquid Ibuprofen the body temperature was 101.95°F after 15 minutes(T1), 101.20 $^0$F after 30 minutes(T2), 100.14 $^0$F after 60 minutes(T3), 99.60$^0$F after 90 minutes(T4), 99.79 $^0$F after 120 minutes(T5), 99.35$^0$F after 150 minutes(T6) and 99.25$^0$F after 3 hours(T7).

# CHPTER 6

# Discussion

## 6.1Discussion

Fever is a complex, coordinated autonomic, neuroendocrine, and behavioral response. It usually occurs in response to a variety of infectious organisms and non infectious inflammatory conditions. For an adult, a fever may be uncomfortable, but usually isn't dangerous unless it reaches 103 F (39.4 C) or higher. For young children and infants, a slightly elevated temperature may indicate a serious infection. Fever which means a body temperature above the usual range of normal can be caused by abnormalities in the brain itself or by toxic substances that affect the temperature regulating centers (Guyton and Hall, 2003).

The treatment of fever is to restore the abnormal hypothalamic thermo stasis. For this, a variety of NSAIDs (i.e., aspirin, paracetamol, Ibuprofen, mefenamic acid, nimesulide, and ibuprofen-paracetamol combination) are used (Jeremy N Anderson et al, 2002).

Fever is the most common reason for children's presenting to a medical practitioner. It cannot be emphasized too strongly that the individual medical practitioner must answer the basic question: "What is the cause of fever in this patient?" Sometimes, identifying diagnostic patterns of fever will assist in answering this question. The practitioner should have a basic understanding of the mechanisms of fever and the effects of fever on the body.

An oral dose of 7.5 to 10mg/kg of Ibuprofen typically results in peak plasma concentrations within 15 to 30 minutes, which is effective to reduce the body temperature (Lynne C. Kramer et.all, 2008).

Reduction of fever in children and the maintenance of a comfortable state are important to caretakers and primary physicians. Antipyretic use therefore plays a major role in daily pediatric practice, and it must be effective and safe. The most commonly prescribed pharmacologic regimen consists of Ibuprofen every 6-8 hours according to the manufacturer's instructions.

The plasma levels of ibuprofen in 153 febrile children for 6 hours after a single dose of ibuprofen (5 or 10 mg/kg) was measured by RD Brown et al and they found that, Cmax occurred about 2 1/2 hours before maximum antipyresis. At the time when Ibuprofen shows the

antipyretic effect, the plasma concentration of Ibuprofen was 25 to 50% less than Cmax (RD Brown et al, 1992).

Ibuprofen has a plasma halflife of 2 hours (G. Katzung, 2001).

Ibuprofen has a dose-dependent duration of action of approximately 4–8 hours, which is longer than suggested by its short half-life (KD Tripathi,2008).

In our study the body temperature was recorded from 16 patients enrolled in the Institute of Child Health and Shishu Sasthya Foundation Hospital (ICH&SSF). Among them 12 patients were less than 5 years (60 months) and others were older than 5 years.

In general, all patients were given 7.5 to10mg/kg dose of the liquid preparations of Ibuprofen. After administering the dose, it starts to show effectiveness within 15 minutes. It takes about 2 hours and 30 minutes to reduce the body temperature from 101.92$^0$F to 99.00$^0$F. After two hours the temperature starts to increase slightly.

The patients (aged less than 60 months) were given 10 mg/kg dose of liquid Ibuprofen as a single dose. The temperature of patients at the time of administration of Ibuprofen was 102.00$^0$F. After 15 minutes the temperature reduces to 101.95$^0$F. After 30 minutes the body temperature was 101.20$^0$F (Figure: 4.10). It takes about 3 hours to reach the lowest body temperature 99.25°F after administration of liquid Ibuprofen. In some cases the temperature increases slightly after 1:30 to 2:00 hours of the administration of Ibuprofen because the terminal half life of the drug is 1 to 2 hours.

By observing the antipyretic effects of Ibuprofen, it can be said that the Ibuprofen is capable to reduce the body temperature of febrile patients.

# CHAPTER 7

# Conclusion

## 7.1Conclusion

The antipyretic action of Ibuprofen is useful in febrile patients. After administration of liquid Ibuprofen the body temperature of the febrile patients started to fall from 101.92°F to 99.00°F. It takes 2 hours and 30 minutes to reduce the body temperature and after 3 hours the body temperature increases to 99.29°F.

In case of the patients less then the age of 60 months administration of Ibuprofen reduces the body temperature from 102°F to 99.25° F within 3 hours.

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