# Study on effect of Ibuprofen for remission of fever in hospitalized young children (age ≤4yrs/48 months)


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# Study on Ibuprofen for remission of fever in hospitalized young children (age ≤4yrs/48 months)

A study paper submitted to the Department of Pharmacy, East West University in conformity with the requirements for the degree of Bachelor of Pharmacy

A Collaborative study between Department of Pharmacy, East West University and Institute of Child Health and Shishu Sasthya Foundation(ICH&SSF)

# CERTIFICATE

This is to certify that, the thesis 'Effect of Ibuprofen on remission of fever of hospitalized children age ≤48 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 Mithu kumar majumdar (ID: 2005-1-70-033) 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 (Propionic Acid derivative) 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 greater than 4 year. Materials and **methods:** Thirty-two subjects aged less than 1 year 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 Ibuprofen preparation. The patients were given 5 to 10-mg/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 $102^0$F to $99.12^0$F. It takes about 2 hours to decrease the body temperature and after 3 hours the body temperature increases to $99.5^0$F. **Conclusion:** Liquid preparation of Ibuprofen has effect of lowering body temperature of the febrile children.


Key words: Ibuprofen, Febrile, convulsions, liquid preparation, T-test.

List of contents


# Chapter1: Introduction

Definition

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 (Gyton 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 (Gyton 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 (Gyton and Hall, 2003).

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

Measurement and normal variation

When a patient has or is suspected of having a fever, that person's body temperature is measured using a thermometer. At a first glance, fever is present if:

- Temperature in the anus (rectum/rectal) is at or over 37.8 °C (100.0 °F)
- Temperature in the mouth (oral) is at or over 37.5 °C (99.5 °F)
- Temperature under the arm (axillary) is at or over 37.2 °C (99.0 °F)
- Temperature in the ear (otic) is at or over 37.2 °C (99.0 °F)

## Pathophysiology of fever

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 (Gyton and Hall,2003).

Many proteins, breakdown products of proteins, and certain other substances, especially lipopolysaccharide 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 (Gyton and Hall,2003).

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

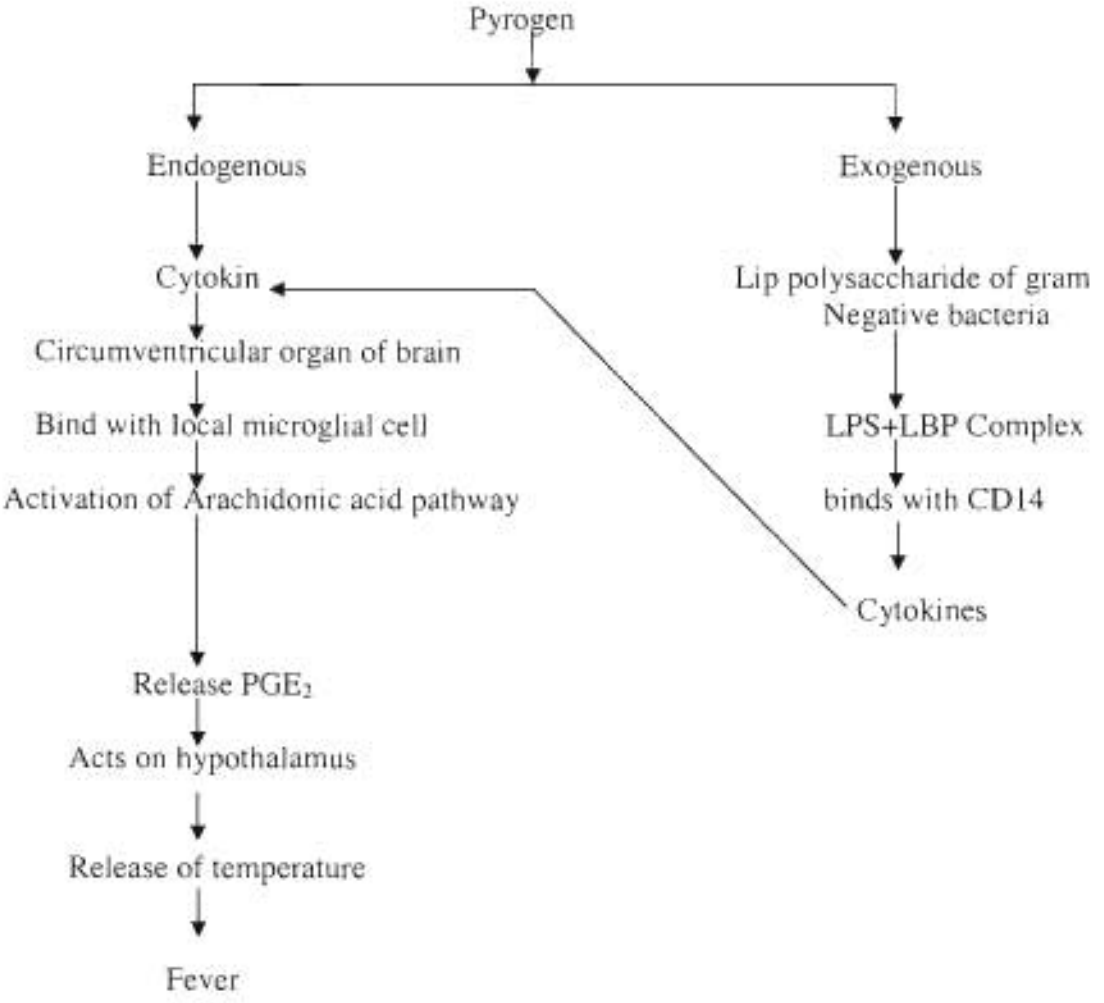



*Fig 1:* Mechanism action of generation of fever

Endogenous Pyrogen

Cytokinase, especially interleukin 1, are a part of the innate immune system, are produced by phagocytic cells, and cause the increase in the thermoregulatory set-point in the hypothalamus. Other examples of endogenous pyrogens are interleukin 6 (IL-6), and tumor necrosis factor-alpha (Gyton 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 microglial cells. When these cytokine factors bind, the arachidonic acid pathway is then activated(Goodman & Gillman,2001).

Exogenous pyrogen

One example for the mechanism of fever caused by exogenous pyrogens includes lipopolysaccharide(LPS), which is a cell wall component of gram-negativ 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 granulers killer lymphocytes.All these cells in turn digest the bacterial products and then release into the body fluids the substences interleukin 1 (IL-1), interleukin 6 (IL-6), and the tumor necrosis factor-alpha. These substences on reaching the hypothelamus, immidiately activates the processes to produce fever, sometimes increases the body tempereture a noticible 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 synthase. These enzymes ultimately mediate the synthesis and release of PGE2(Goodman & Gillman,2001).

The cytokinase increases the secretion of PGE2, via increases in cyclic AMP, triggers the hypothelamus to elevate body tempereture by promoting increases in heat generetion and dicreases heat loss (Goodman & Gillman,2001).

Characteristics of febrile condition

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

Chills

When the set point of the hypothelamic 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. 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 hypothelamic temperature controller, the usual responses that cause elevation of body tmperature occur. During this period, the person experiences chills and feels extremly cold, even though his\her body temperature may already be above normal. Chills can contineu until the body temperature reaches the hypothelamic set point of 103 F(Gyton and Hall,2003).

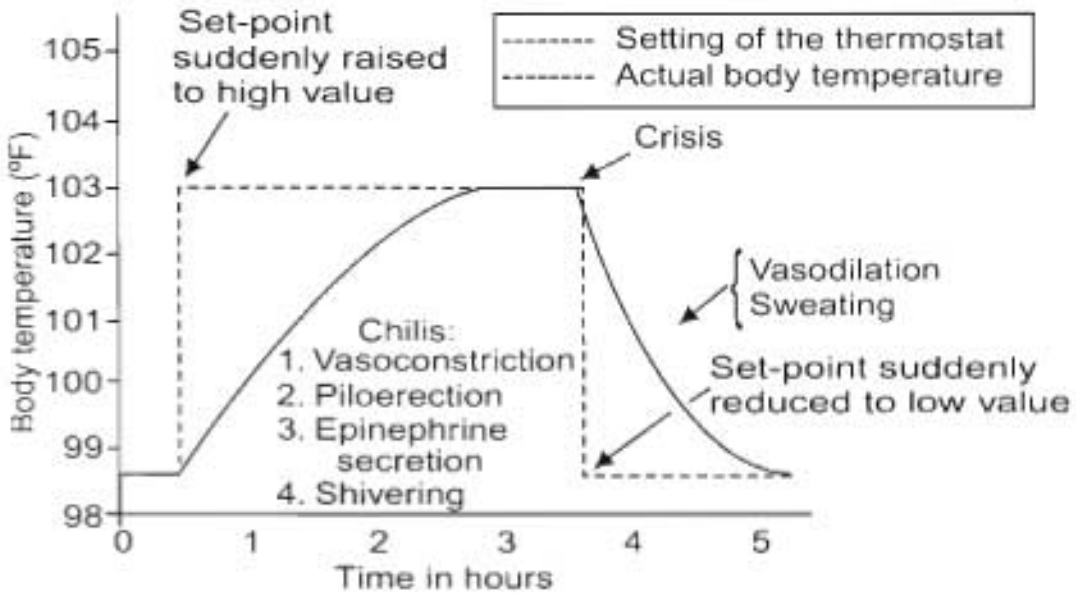



*Fig 2:* Different stages of fever

The Crisis or Flash

If the factor that causing the high temperature is suddenly removed, the set point of the hytpothelamic temperature controller is suddenly reduced to a lower value, perhaps even back to the normal level. In this instance the body temperature is still 103 F, but the hypothelamus is attempting to regulate the temperature to 98.6 F. This situation is analogous to execive heating of the anterior hypothelamic preoptic 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 (Gyton and Hall,2003).

Fever Classification

Most of the time, fever types can not be used to find the underlying cause. However, there are specific fever patterns that may occasionally hint the diagnosis:

- Pel-Ebstein fever: A specific kind of fever associated with Hodgkin's lymphoma, being high for one week and low for the next week and so on.
- Continuous fever: Temperature remains above normal throughout the day and does not fluctuate more than 1 °C in 24 hours, *e.g.* lobar pneumonia, typhoid, urinary tract infection, brucellosis, or typhus.
- Intermittent fever: Elevated temperature is present only for some hours of the day and becomes normal for remaining hours, *e.g.* malaria, kala-azar, pyaemia, or septicemia.
- Remittant fever: Temperature remains above normal throughout the day and fluctuates more than 1 °C in 24 hours, *e.g.* infective endocarditis

A neutropenic fever, also called febrile neutropenia, is a fever in the absence of normal immune system function. Because of the lack of infection-fighting neutrophils, a bacterial infection can spread rapidly and this fever is therefore usually considered a medical emergency. This kind of fever is more commonly seen in people receiving immune-suppressing chemotherapy than in apparently healthy people.Febricula is a mild fever of short duration, of indefinite origin, and without any distinctive pathology.

## Ibuprofen

Ibuprofen is an NSAID (non-steroidal anti-inflammatory drug) that is commonly used for the relief of symptoms of arthritis, fever, primary dysmenorrhea (menstrual pains), and as an analgesic (a medication given to reduce pain without resulting in loss of consciousness). Ibuprofen also has an antiplatelet effect (protects from blood clots), though less than aspirin. The World Health Organization (WHO) includes ibuprofen in its "Essential Drugs List"; a list of minimal medical needs for a basic health care system.

History of ibuprofen

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 a 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.

*Table 1*: Prominent brand of Ibuprofen suspension in Bangladesh

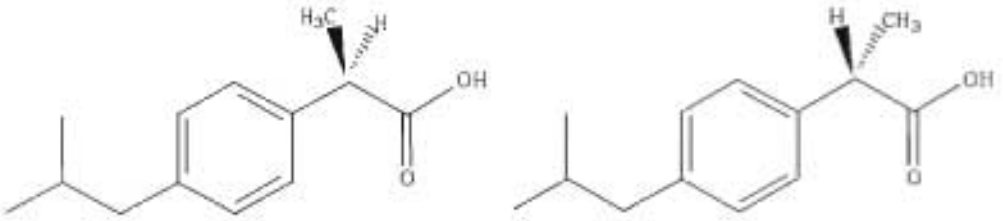
| Brand name | Company |
|---|---|
| Inflam | Aventis |
| Profen | ACME |
| Rumafen | Beximco |
| Flamex | ACI |
| Al- flam | Albion |

*Table 2*: Internation brand of Ibuprofen suspension

| Brand Name | Company | Country |
|---|---|---|
| Bifen | DHA (Drug house of Australia) | Australia |
| Infacalm | Tianda | Hong kong |
| Nurofen | Reckitt and benckiser | Hong kong |

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

*Fig 3:* S and R form of 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. (4)

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

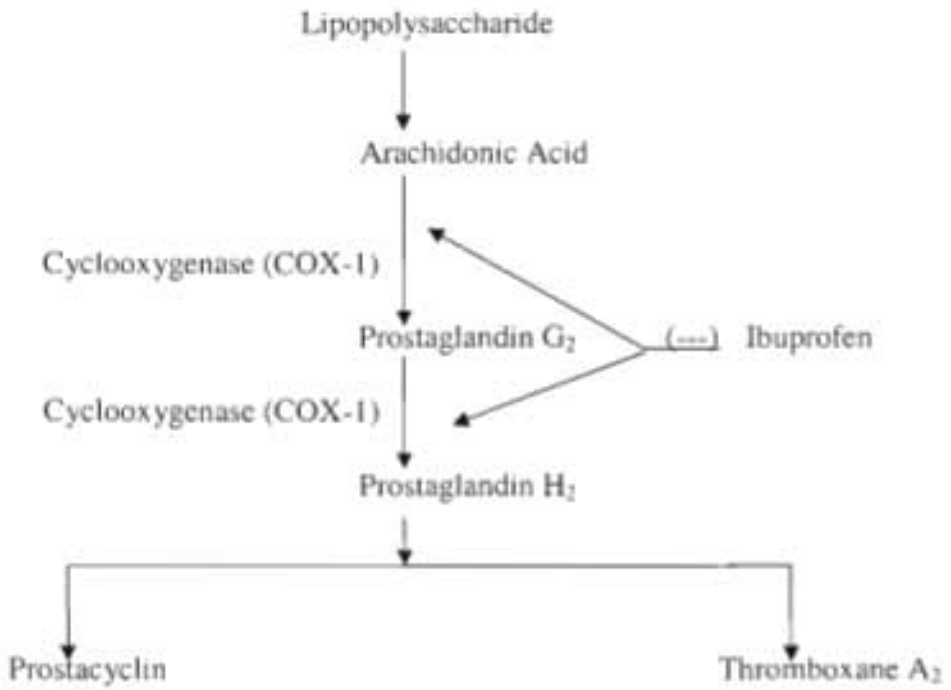



*Fig 4:* Mechanism of action of Ibuprofen

Ibuprofen also has anti-inflammatory properties, and it belongs to a class of therapeutic agents known as nonsteroidal anti-inflammatory drugs, or NSAIDs. Like another NSAID, acetaminophen and ibuprofen works by inhibiting the activity of a class of enzymes called cyclooxygenases (COX).

One of the most interesting things about human COX enzymes is that there is more than one of them—definitely two, and probably at least three. This is important to our understanding of the therapeutic effects of ibuprofen, aspirin, and acetaminophen. It had long been suspected that there was more than one COX enzyme, but it was not until 1991 that evidence for the existence of two forms, COX-1 and COX-2, materialized. 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 and aspirin (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 and aspirin both inhibit COX-1 and COX-2, but they do it in different ways. Ibuprofen binds noncovalently to a COX enzyme and thus competes with the enzyme's natural substrate.

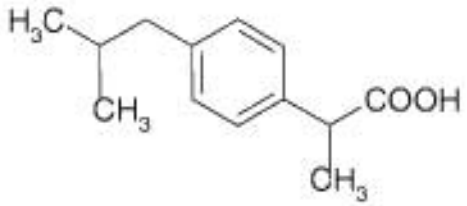



*Fig 5:* Structure of ibuprofen.

On the other hand, aspirin forms a covalent bond to a serine residue in the enzyme, and this bond cannot be broken. (This is called irreversible inhibition.) Acetaminophen does not interact with either COX-1 or COX-2, but it is now understood that it may interact with a newly identified cyclooxygenase, COX-3. Selective targeting of the COX enzymes

is an exciting area of pharmacology, in which the challenge continues to be the development of drugs that interact with specific COX enzymes.

Pharmacokinetics and metabolism

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.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.

Metabolism occurs via hepatic bio transformetion. Metabolism involve Cytochrome P450 2C9 (CYP2C9) and Monoamine oxidase type B (MAO-B) enzymes.

The excretion of ibuprofen is rapid and complete. More thn 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.

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%) interconverted into the active [+]S species in adults. 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.

Absorption

The ibuprofen is well absorbed orally from the suspension formulation and peak plasma levels occur within 1 to 2 hours. Absorption is most rapid when Ibuprofen is given under fasting conditions.

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. Metabolism

Following oral administration, the majority of the dose was recovered in the urine within 24 hours as the hydroxy-(25%) and carboxypropyl-(37%) phenylpropionic acid metabolites. The percentages of free and conjugated ibuprofen found in the urine were approximately 1% and 14%, respectively. The remainder of the drug was found in the stool as both metabolites and unabsorbed drug.

Ibuprofen is administered as recemic mixture. After administration the R-form is converted into

S-form in liver by following pathway.

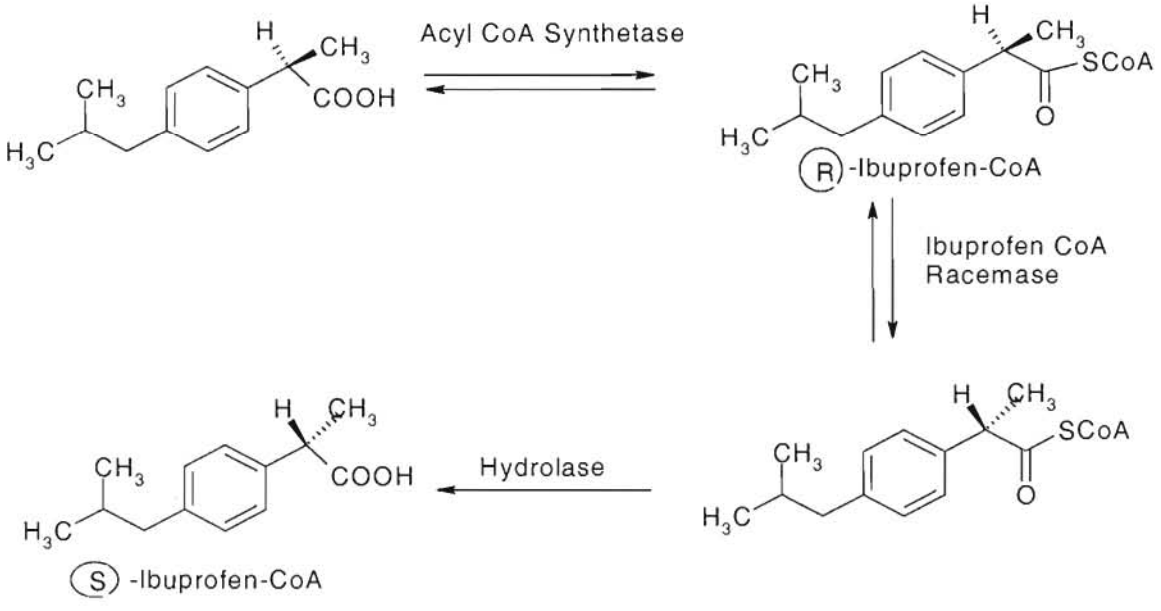



*Fig 6:* Metabolic pathway of Ibuprofen active form.

Hydroxylation of the isobutyl side chain at the subterminal 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

Elimination

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.

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.

For antipyratic action, daily doses of 1200 mg for adults and 800 mg for children, in divided portions may be givn.For rheumatoid arthritis and ostearthritis, daily doses of up to 3200mg in divided portions may be givn, 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, specially that of primary dismenorrhoea, the usual dosage is 400 mg every 4 to 6 hours as needed.

Uses of Ibuprofen

- Ibuprofen is used as asimple analgesic and antipyretic. It is particularly effective in dysmenorrhoea in which the action is clearly due to PG synthesis inhibition. It is available as an OTC drug (KD Tripathi,2003).
- Ibuprofen is widely used in rheumatoid arthritis, osteoarthritis and other musculoskelital diseorders, specially where pain is more prominent than inflammetion(KD Tripathi,2003).

- Ibuprofen is indicated in soft tissue injuries, fractures, vasectomy, tooth extraction, postpartum and post operatively: suppress swelling and inflammetion(KD Tripathi,2003).

Side effects

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

- Gastrointestinal side effects experienced by 5% to 15% of petients taking ibuprofen. Common gastro intestinal side effects include: epigastric pain, nausea, heart burn,and sensetion f fullness in gastrointestinal drug(KD Tripathi,2003).
- 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,2003).


Side Effects by Body System

Gastrointestinal

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. et al, 997).

Anti-platelet

Inhibition of synthesis of thromboxane A2 by platelets that results prolonged bleeding

time and GI bold loss (Charles R. et al, 997).

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. et al, 997).

Allergic

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

Uterine

Loss of contractile effects of PGs on uferine muscles. That results delayed parfurition dystocia (Charles R. et al, 997).

## Literature review of ibuprofen on the fever patient

The study of double-blind (Fever Co-operative Group from the Spanish Paediatric Association, 2002) was to assess the pediatrics antipyretic efficacy of a new ibuprofen formulation containing L-arginine for gastric protection, compared with the efficacy of paracetamol. In this study100 patients were given ibuprofen-arginine (1 drop/kg: 6.67 mg/kg) and 99 patients were given paracetamol (4 drops/kg: 10.65 mg/kg) the main efficacy was taken after 4 hr administration. The study uses 88 patients treated with ibuprofen-arginine and 87 with paracetamol.Overall analysis efficacy to improve in 68.8% of patients in the ibuprofen-arginine group compared with 65.5% in the paracetamol group and few patient have adverse effect such as vomiting and othe common complaint. On the base of the study results, ibuprofen-arginine oral drops have shown to be a safe, well-tolerated and potent paediatric antipyretic agent (Figueras Nadal C, 2002).

The community health practitioners frequently prescribe or advise parents on antipyretic two medications - paracetamol and ibuprofen for children with fevers and literature

search was to comparing the effects of the two drugs. The Medline, Embase, Cinahl and RCN collect databases were eight randomized controlled trials that temperature at differences at time-interval between 1 and 6 hours after administration. They never found any clear evidence for one drug over another 1 hour but 6 hours after administration ibuprofen was clearly superior to reduce temperature. On the two drugs are effective antipyretics and longer action of ibuprofen then paracetamol after administration (Purssell E, 2002).

The objective of the studies testing the efficacy and safety of single-dose acetaminophen and ibuprofen for treating children fever and databases were taken (from their inception through May 2002) and registries, relevant journals, and bibliographies of key articles. Ibuprofen (4-10 mg/kg) and acetaminophen (7-15 mg/kg) showed comparable efficacy (3 pain relief trials; 186 children).Ibuprofen (5-10 mg/kg) reduced temperature more than acetaminophen (10-15 mg/kg) at 2, 4, and 6 hours after treatment .So Ibuprofen (5-10 mg/kg) was a more effective antipyretic than acetaminophen (10-15 mg/kg) at 2, 4, and 6 hours post treatment (Perrott DA,2004).

Antipyretics reduce the prolonged high fever characteristic of typhoid fever treated with nonsteroidal drugs such as ibuprofen and paracetamol. In this double blind randomized study, 80 patient children suffer typhoid fever were to receive identical syrup preparations of ibuprofen (10 mg/kg) or paracetamol (12 mg/kg) every 6 h until 36 h after defervescence. The fever clearance time (hours) was shorter in the ibuprofen group than the paracetamol group. The antipyretic effect of ibuprofen is superior to that of paracetamol in children with typhoid fever, particularly those with prolonged fever. Both antipyretics appeared to be safe (Vinh H, 2004).

The medication of acetaminophen or ibuprofen of both drugs in young children aged 6 to 36 months and use of 464 patient databases collected three primary pediatric community ambulatory centers in central Israel. Infants were administered acetaminophen (12.5 mg/kg per dose every 6 hours) (n = 154) or ibuprofen (5 mg/kg per dose every 8 hours) (n = 155) or to receive alternating acetaminophen and ibuprofen (every 4 hours) (n = 155) for 3 days after a loading dose. The group was characterized by a lower mean temperature, more rapid reduction of fever, receiving less antipyretic medication and less stress compared with the other groups. The treatment of acetaminophen (12.5 mg/kg per

dose) and ibuprofen (5 mg/kg per dose) every 4 hours for 3 days more effective of ibuprofen lowering fever in infants and children (Sarrell EM, 2006).

In case of safety and efficacy equal doses ibuprofen appears slightly more effective than acetaminophen in the treatment of fever. These data suggest there is an increased risk of invasive group A streptococcal infection after chickenpox and of acute renal failure in case of hypovolemia after a treatment by ibuprofen. Gastro duodenal and hemorrhagic adverse events could also happen, but the causality with ibuprofen is not demonstrated. So ibuprofen is more effective the treatment of fever or moderate pain during chickenpox or during a disease with a risk of dehydration, until other pharmaco-epidemiology studies more accurately quantify the risk of adverse events of ibuprofen in children (Leroy S, 2007).

The aim was the tolerability and safety between ibuprofen and paracetamol when used as anti-pyretic and analgesic agents in children up to 18 years of age.The analysis of data tolerability and safety of ibuprofen was similar to placebo, ibuprofen versus placebo relative risk (RR) 1.39 in 21305 patients and paracetamol versus placebo RR 1.57 in11164 patient. There was no significant difference between the two groups. Ibuprofen and paracetamol have similar tolerability and safety profiles in terms of gastrointestinal symptoms, asthma and renal adverse effects. The study data investigated that safety concerns relating to general ibuprofen or paracetamol treatment in children (Southey ER, 2008).

The double-blind control study comparing the efficacy of acetaminophen alternated with ibuprofen in administered 38 patient at the age 6month to 6 years at the 100.4°F.and temperatures were recorded time at 0, 3, 4, 5, and 6 hours. There were no significant differences in temperature between the 2 groups at times 0, 3, and 6 hours. The alternating group had significantly lower mean temperatures at both 4 hours and 5 hours. They did not found any difference in fever control between the groups. So acetaminophen with ibuprofen significantly decreased fever at 4 and 5 hours compared with acetaminophen alone (Kramer LC, 2008).

*Table 3:* Literature review of Ibuprofen on Fever

| Year | Name of Publisher | Finding |
|---|---|---|
| 2002 | Figueras Nadal C | Effectiveness and tolerability of ibuprofen arginine versus paracetamol in children with fever of likely infectious origin.Infectious Disease Section |
| 2002 | Purssell E | Treating fever in children: paracetamol or ibuprofen |
| 2004 | Perrott DA | Efficacy and safety of acetaminophen vs ibuprofen for treating children's pain or fever: a meta-analysis |
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# Chapter 2

## Materials and Methods

Hypothesis

After administration of liquid preparation of ibuprofen, the body temperature of children ≤4yrs/48 month will be reduced.

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 ≤4yrs/48 month.
- Whether the ibuprofen liquid preparations have any effect on the febrile patient or not.

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. (Hewson P, Paediatrician, Geelong, Vic, 2000).

Liquid preparation of ibuprofen is effective in reducing fever in hospitalized young children (≤4yrs/48 month)

Research Design

19 patients with Fever were enrolled in the study ≤ 4yrs/48 month

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). Nineteen subjects meeting the following inclusion and exclusion criteria were sampled:

Inclusion criteria:

- Patient : Fever
- Age : Above 6 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.

Study Period

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

Patient's personal information

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

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.


*Fig 7:* 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 (axillary) or rectal method.
Underarm (Axillary) Method: This method for babies or very young children. Although simpler, the axillary 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 axillary 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.

Statistical Analysis:
Data were analyzed using SPSS for widow's 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.

# Chapter 3

## Result, discussion and conclusion

Percent distribution of fever among the male and female patients (n=19).

From the clinical trial of Ibuprofen suspension was administered with 19 patients (n=19). Where no of male patients were 12(63.16%) and no f female patients were 7(36.84%).So Figure shows 63% male and 37% female patients have suffered from fever.

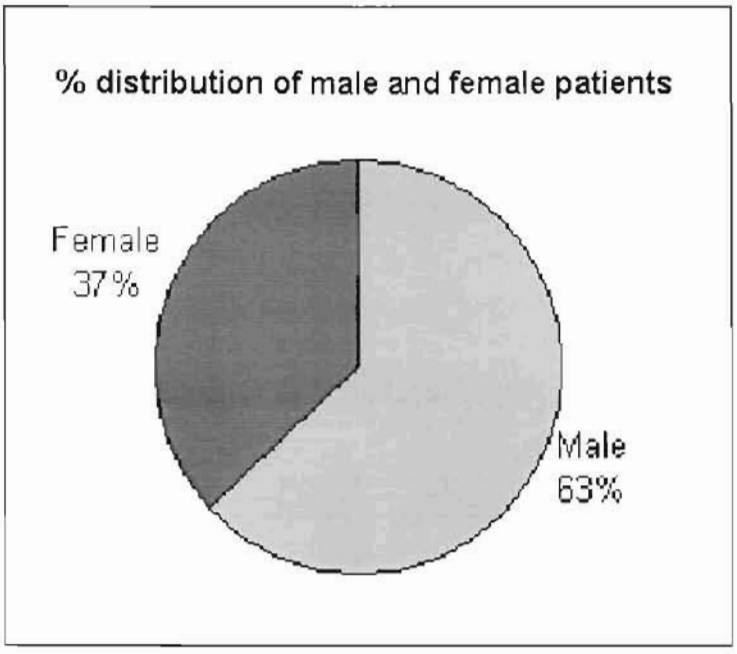


*Fig 8:* representing the percent distribution of male and female patients.

Number of the patients with fever according to the sex and different age groups (n=19)

Age of the 1 male and patients in the study group is within the range of 0-12 months. Six, one, zero, one, one, two, zero, zero male patients were in the range 13-24, 25-36,37-48,49-60,61-72,73-84 and above 96 months respectively. Ages of no female patients were in the range of 0-12 months. Three , zero, zero, one, zero, zero, zero, two female patient in the range 13-24, 25-36, 37-48,49-60,61-72,73-84 and above 96 months respectively.

*Table 4:* shows that Number of the fever patients according to the sex and different age groups

| 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=12) | 1 | 6 | 1 | 0 | 1 | 1 | 2 | 0 | 0 |
| Female (n=7) | 0 | 3 | 0 | 0 | 1 | 0 | 0 | 0 | 3 |

Comparison of the effect of Ibuprofen on male and female febrile patients (n=19)

Figure 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 101.9° F and the mean temperature after 3 hours was 99.3° F. In case of female the mean temperature at the time of drug given was 102.3° F and after 3 hours it was 99.7°.

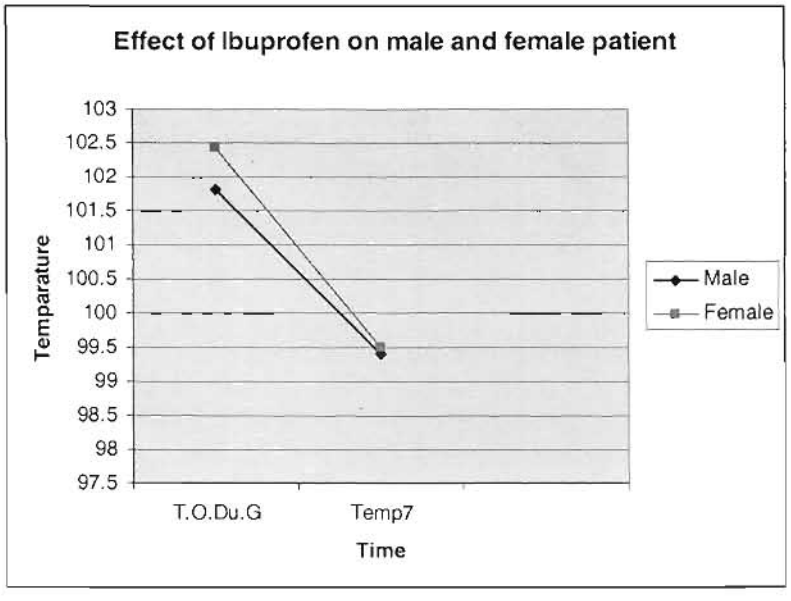


*Fig 9:* Comparison of the effect of Ibuprofen on male and female febrile patients

Mean age (months) of male and female patients with fever (n=19).

The mean age of the male is 37.75 ± 28.84 and female is 60.57± 47.86

*Table 5:* The mean age (months) of male and female patients with fever

| Sex | Mean Age (month) ± SD |
|---|---|
| Male (n=12) | 37.75 ± 28.84 |
| Female (n=7) | 60.57± 47.86 |

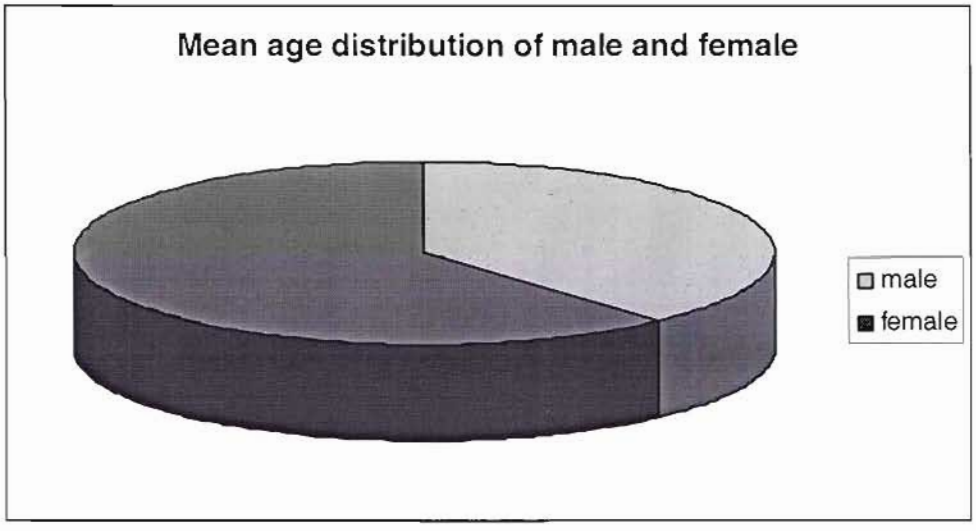


*Fig 10:* represents that Mean age distribution of male and female (n=19)

From the above graph is representing the mean age of male patients is 37.75 ± 28.84 and the female patient is 60.57± 47.86.

Mean temperature of the patients with fever at different time intervals (n=19)

*Table 6:* shows the mean body temperature of the patients with fever at different time intervals.

| Time | Mean temperature ± SD (°F) |
|---|---|
| Before drug administered | 102.03 |
| After 15 minutes | 101.88± .94* |
| After 30 minutes | 101.19 ± 1.10* |
| After 1 hour | 101.25 ±1.08 * |
| After 1.5 hour s | 99.68±1.47* |
| After 2 hours | 99.67 ±1.90 * |
| After 2.5 hours | 99.35±1.36 * |
| After 3 hours | 99.44± 1.48* |

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

Body temperature of the patients with fever at different time intervals (n=19).

Figure shows the body temperature of the patients at different time intervals. The body temperature of the patient was 102.03$^0$F before administration of the liquid Ibuprofen. After administration of liquid Ibuprofen the body temperature was 101.88$^0$F after 15 minutes, 101.19$^0$F after 30 minutes, 100.25$^0$F after 60 minutes, 99.68$^0$F after 90 minutes, 99.67$^0$F after 120 minutes, 99.36$^0$F after 150 minutes and 99.44$^0$F after 3 hours.

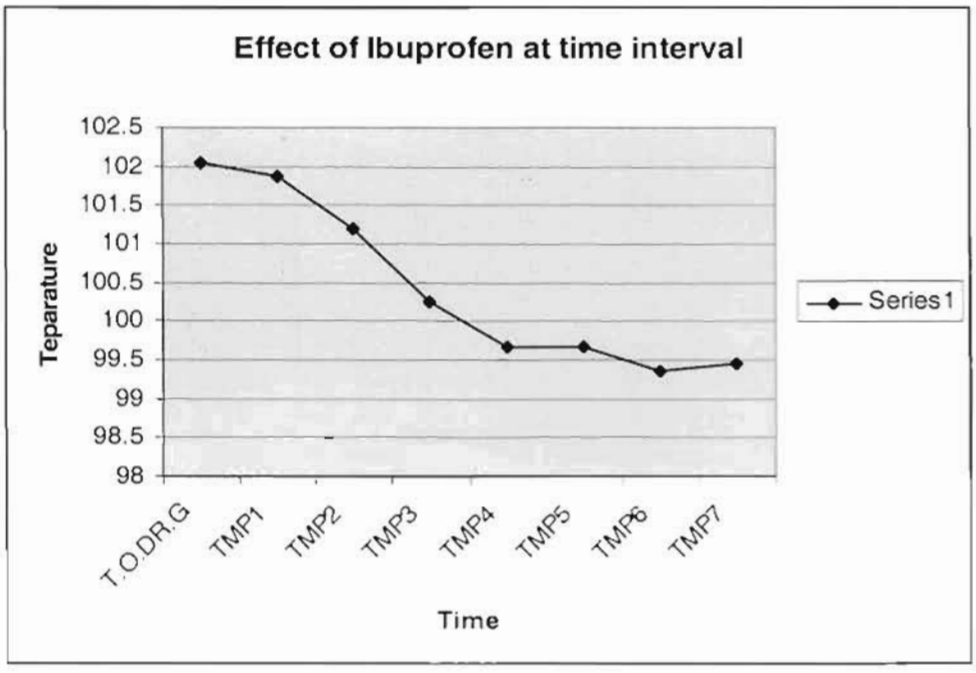


*Fig 11:* shows that Effect of ibuprofen at time interval (n=19)

Percent distribution of Fever among the male and female patients aged ≤4year/48 month (n=11).

From the clinical trial of Ibuprofen suspension was administered with 11 patients (n=19). Where no of male patients were 8 (72.73%) and no f female patients were 3(26.23%).So Figure shows 27 % male and 73% female patients have suffered from fever.

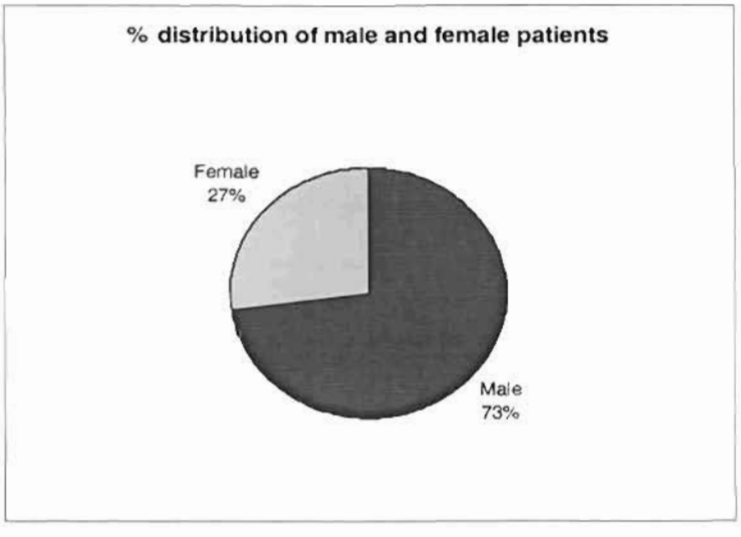


*Fig 12:* representing the percent distribution of male and female patients aged ≤4year/48 month (n=11).

Number of the patients with fever according to the sex and age ≤4year/48 month (n=11)

Age of the 1 male and patients in the study group is within the range of 0-12 months. Six, one, zero, male patients were in the range 13-24, 25-36 and above 37-48 months respectively. Ages of no female patients were in the range of 0-12 months. Three, zero, zero female patient in the range 13-24, 25-36, and above 37-48 months respectively.

*Table 7*: Number of the patients with fever according to the sex and age ≤4year/48 month (n=11)

| Sex | 0 to 12 month | 13to 24 month | 25 to36 month | 37 to48 month |
|---|---|---|---|---|
| Male (n=12) | 1 | 6 | 1 | 0 |
| Female n=7) | 0 | 3 | 0 | 0 |

Mean age (≤4yrs/48months) of male and female patients with fever (n=11).
The mean age of the male is 19.13 ± 7.83and female is 13.33± 2.52

*Table 8:* The mean age (≤4yrs/48months) of male and female patients with fever

| Sex | Mean Age (month) ± SD |
|---|---|
| Male (n=8) | 19.13 ± 7.83 |
| Female (n=3) | 13.33± 2.52 |

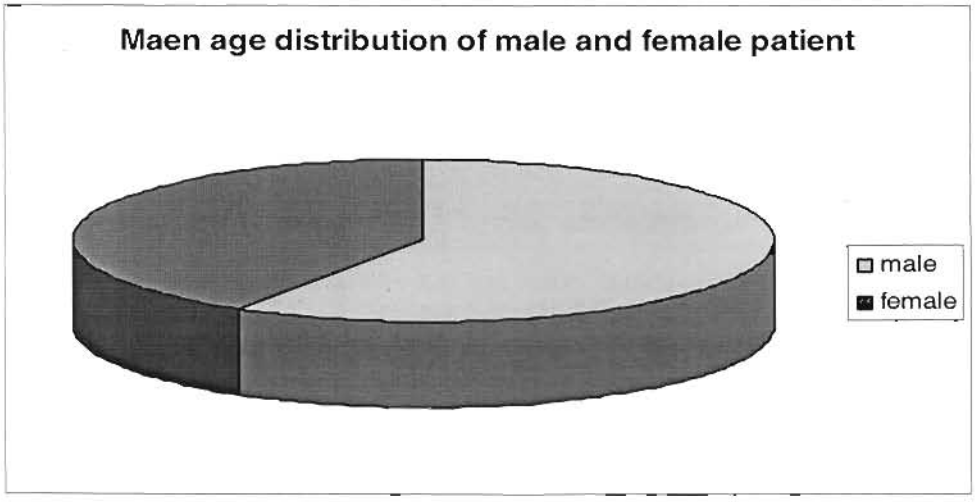


*Fig 13:* represents that Mean age distribution of male and female patient

From the above graph is representing the mean age of male patients is 19.13 ± 7.83and the female patients are 13.33± 2.52.

Mean temperature of the patients with fever at different time intervals age ≤4year/48 month (n=11)

*Table 9*: 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± .99* |
| After 30 minutes | 101.23± 0.99* |
| After 1 hour | 100.15 ±0.98 * |
| After 1.5 hour s | 99.56±1.42* |
| After 2 hours | 99.32 ±1.40 * |
| After 2.5 hours | 99.23±1.22* |
| After 3 hours | 99.13± 1.32* |

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

Body temperature of the patients with fever at different time intervals age ≤4year/48 month (n=11).

Figure shows the body temperature of the patients at different time intervals. The body temperature of the patient was 102.01$^0$F before administration of the liquid Ibuprofen. After administration of liquid Ibuprofen the body temperature was 101.95$^0$F after 15 minutes, 101.23$^0$F after 30 minutes, 100.15$^0$F after 60 minutes, 99.56$^0$F after 90 minutes, 99.32$^0$F after 120 minutes, 99.23$^0$F after 150 minutes and 99.13$^0$F after 3 hours.

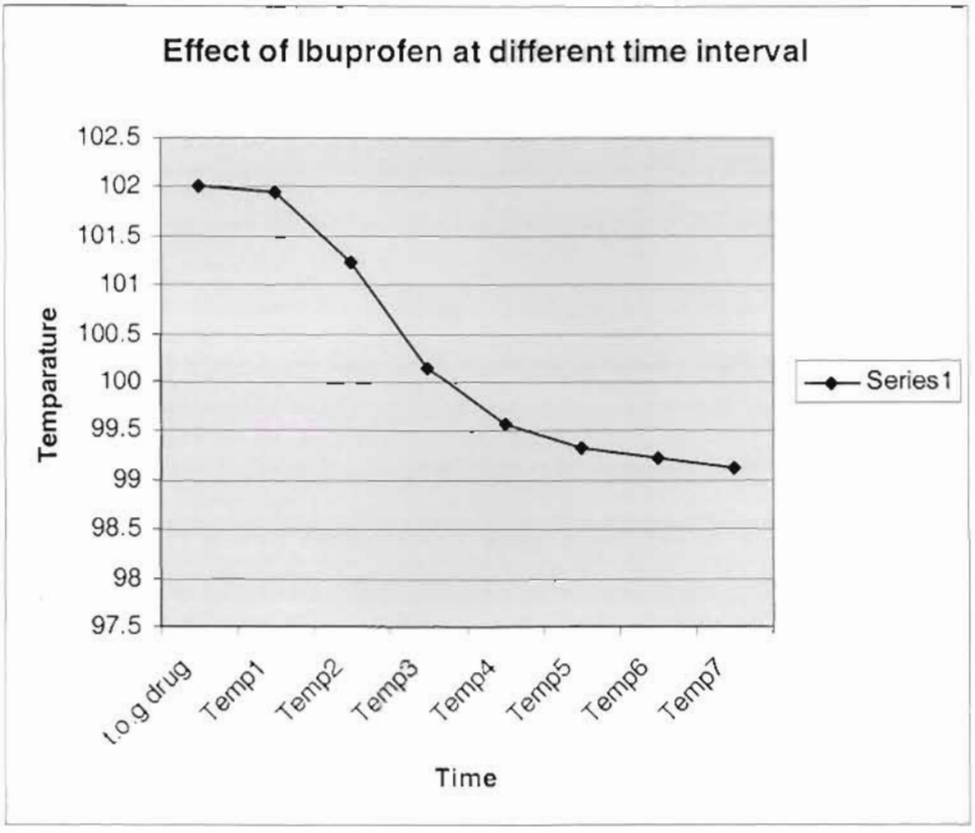


*Fig 14:* represents that Body temperature of the patients with fever at different time intervals age ≤4year/48 month (n=11).

## Discussion

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 (Gyton 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, Diclofenac, 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 to 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 19 patients enrolled in the Institute of Child Health and Shishu Sasthya Foundation Hospital (ICH&SSF). Among them 11 patients were less than 4 years (48 months) and others were older than 4 years.

In general, all patients were given 5 to10mg/kg doses 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 $102.03^0$F to $99.35^0$F. After two hours the temperature starts to increase slightly.

The patients (aged less than 48 months) were given 5 to 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 $101.23^0$F. It takes about 3 hours to reach the lowest body temperature 99.12°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.

## Conclusion

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 102.3°F to 99.35°F. It takes 2 hours and 30 minutes to reduce the body temperature and after 3 hours the body temperature increases to 99.44°F.

In case of the patients less then the age of 48 months administration of Ibuprofen reduces the body temperature from 102°F to 99.12° F within 3 hours.

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