International Journal of Medical Research & Health Sciences

www.ijmrhs.com Volume 2 Issue 1 Jan-Mar 2013 Coden: IJMRHS Copyright @2013 ISSN:2319-5886

Received: 4th Nov 2012 Revised: 3rd Dec 2012 Accepted: 7th Dec 2012

Original research article

EVALUATION OF EFFICACY AND TOLERABILITY OF ACETAMINOPHEN (PARACETAMOL) AND MEFENAMIC ACID AS ANTIPYRETIC IN PEDIATRIC PATIENTS WITH FEBRILE ILLNESS: A COMPARATIVE STUDY.

*Kunkulol Rahul R[1], Sonawane Aishwarya[2], Ashok Kumar Chavva[3]

[1]Associate Professor, Department of Pharmacology, Secretary, Research Cell, PIMS-DU, Loni.
[2]UG, Rural Medical College, Loni.[3]Professor, Department of Pediatrics, Rural Medical College, Loni

*Corresponding author e mail: rahul4420@yahoo.com

ABSTRACT

Objectives: With the increase in reports of the failure of Paracetamol as antipyretic in pediatric patients and the increase in the use of Mefenamic acid, the study was undertaken to recommend best among the both antipyretics by comparing the efficacy and tolerability of both these drugs.
Methods-It was a prospective, active treatment controlled study with follow up to 72 hours done over a period of 2 months after the Institutional Ethical committee approval. Total 124 pediatric patients with fever admitted to Pravara Rural Hospital, Loni having a body temperature >38.5 and fulfilling the inclusion and exclusion criteria were included. Patients included were categorized into two groups –group A and group B and administered Paracetamol and Mefenamic acid in the doses 15 mg/kg and 4 mg/kg body weight respectively. The parameters essential for comparing the efficacy and tolerability were observed and recorded. The collected data were subjected to 'paired **t** test' of significance and was analyzed statistically.
Results-Both drugs significantly decreased body temperature in pediatric patients with fever. The antipyretic efficacy of Mefenamic acid was highly significant than Paracetamol (<0.05). No significant differences in adverse effects were noted in both the groups. **Conclusion**-Mefenamic acid was found to be more effective and equally tolerable than paracetamol as an antipyretic in pediatric patients with febrile illness and can be the best alternative to paracetamol.

Keywords: Acetaminophen, Mefenamic acid, MTTES.

INTRODUCTION

Fever is one of the most important and common presenting symptom in pediatric clinics, outpatient departments and emergency. [1] Fever may be defined as a complex physiologic response to a disease, mediated by pyrogenic cytokines and characterized by a rise in core temperature, generation of acute phase reactants and activation of immune systems[2]. Regulation of body temperature requires a delicate balance between production and loss of heat, the hypothalamus

regulates the set-point at which the body temperature is maintained. In fever this hypothalamus thermostat set point is elevated and body temperature increases over normal values. The normal range of body temperature is 36.5 ° - 37.5° C.[3]

In most clinical situations, fever results from the presence of the substances called pyrogens. Various infections, toxins and other mediators induce production of pyrogens by host inflammatory cells such as macrophages, endothelial cells and lymphocytes. Best pyrogens are endotoxins (Lipopolysaccharides, LPS) produced by gram negative bacilli. Gram positive bacteria also produce pyrogens as their cell wall has peptidoglycan and Lipoteichoic acid. The endogenous pyrogens produced locally or systemically gain entrance in the circulation and produce fever[1,4]. The major fever causing cytokines are various Interleukins (IL) IL-Iβ, IL-lα, 1L-6, TNF-α (Tumor necrosis factor) and INF-α (interferon). These pyrogenic cytokines directly stimulate the hypothalamus to produce PGE2 (prostaglandin I2) which then resets the temperature regulatory set point. IL-1 is an important pyrogen that on reaching the hypothalamus induces fever in 8-10 minutes time[1].When the pyrogenic cytokines disappear from the circulation or inhibition of cyclooxygenase by the metabolites, the hypothalamus is again reset downward so now the heat dissipation mechanisms come into play causing vasodilation and sweating.

It has been shown beyond doubt that increase in the temperature of the body puts the child under threat of convulsions, dehydration, metabolic acidosis and fever induced stroke. So Antipyresis is one of the most usual therapeutic interventions undertaken.[1]

The most commonly used antipyretics are Nonsteroidal Anti Inflammatory Drugs (NSAIDS), which also have a considerable analgesic effect which promotes a general feeling of well-being. Antipyretic treatment is now routinely prescribed to febrile children, though variedly by most pediatricians.

Antipyresis occurs with different classes of substance including Acetyl Salicylic Acid (ASA), Acetaminophen and the other nonsteroidal anti-inflammatory agents represented by Indomethacin, Mefenamic acid, Ibuprofen and the latest Nimesulide. Some antipyretics are anti-inflammatory. NSAIDs inhibit cyclooxygenase (COX) which catalyzes the conversion of arachidonic acid to prostaglandin E2. This reduction of prostaglandin E2 in the brain is believed to lower the hypothalamic set point.[1, 4]

Aspirin, once a preferred drug is no longer used in reducing fever as it has potential to cause Reye's syndrome. Acetaminophen, Mefenamic acid and Nimesulide are currently three preferred drugs for treating fevers in children.

Acetaminophen (paracetamol) antipyretic is in use for a considerable time. As with ASA, the antipyretic effect of Paracetamol is believed to be caused by its ability to decrease prostaglandin synthesis in the brain. Since Paracetamol does not inhibit the synthesis of prostaglandins in the periphery, it does not possess any anti-inflammatory action. Besides its beneficial effects PCM also has potential side effects and may cause severe hypersensitivity reactions[1,4]. Nimesulide is a non-steroidal anti-inflammatory drug with analgesic and antipyretic properties. Its efficacy has been compared with naproxen, ASA, paracetamol and Mefenamic acid but it is banned due to fulminant hepatitis. Mefenamic acid is a potent inhibitor of cyclooxygenase. It has a central as well as peripheral analgesic action. The drug is commonly used in patients with injuries, osteoarthritis, rheumatoid arthritis and dysmenorrhea. The pediatric suspension of Mefenamic acid is recommended 50mg/5ml or 25mg/kg body weight in divided doses.[3-6]

It is essential to establish a cause for a fever and then provide effective modern treatment. Judicious use of the antipyretics needs to be considered giving due respect to the body's response to the

infection in the form of fever. The decision to choose an antipyretic should be dictated by efficacy, safety, duration of action, effectiveness and cost. [1] PCM has always been a dependable antipyretic and has an additional advantage of being a cheaper drug and relatively safer antipyretic. There have been reports of failure of antipyretic drugs including paracetamol in controlling fever and trends of increase use of Mefenamic acid as antipyretic. Moreover there are no studies comparing efficacy and tolerability of Acetaminophen and Mefenamic acid. Hence it was thought prudent to evaluate both these drugs for better antipyretic efficacy in pediatric patients with febrile illness.

Aims and objectives

1. To compare the efficacy of Acetaminophen (Paracetamol) And Mefenamic Acid in pediatric patients with fever.
2. To compare the tolerability and adverse effect of Acetaminophen (Paracetamol) And Mefenamic Acid in pediatric patients with fever
3. To recommend best antipyretic in pediatric patients.

MATERIALS AND METHODS

This was a prospective observational clinical study done in collaboration with the Department of Pediatrics, Pravara Rural Hospital, Loni. The Institutional ethical committee approval was obtained before the initiation of the study.

Patients diagnosed by Department of Pediatrics with febrile illness were enrolled in the study according to the following inclusion and exclusion criteria. Written informed consent was taken from each patient.

Inclusion criteria

1. Patients ready to give informed consent.
2. Hospitalized children having temperature > 99.6 $^{\circ}$ F
3. Patients 1-12 years.
4. Patients of either sex.
5. Patients of all types of febrile illness.

Exclusion criteria

1. Uncooperative patients.
2. Patients not following the protocol.
3. Patients above the age of 12 years.
4. Patients who were hypersensitive to drugs.
5. Patients having any inflammatory illness
6. Severely ill patients suffering from circulatory collapse, blood dyscrasias, cardiac or hepatic disease, G-6-PD deficiency or meningitis.
7. Children having collagen vascular diseases or malignancy as a primary or the underlying cause of fever and those receiving antimicrobials and/or corticosteroids within 24 hours preceding the study.

Study conduct

This was a prospective, observational, comparative study with follow- up till 72 hours. A total of 124 children having temperature > 99.6 $^{\circ}$ F admitted to the Pediatrics ward, Pravara Rural Hospital, Loni were included in the study.

Enrolled patients were categorized into 2 groups depending on antipyretic treatment given by the pediatricians**:**

Group A: Paracetamol treated at a dose of 15 mg/kg given as suspension [1, 10]

Group B: Mefenamic acid 4 mg/kg given as a suspension. [8]

Following parameters were recorded in each group for:

1. **Efficacy evaluation**[7]

Axillary temperature (measured with a mercury thermometer)

- Before drug administration
- Every 1 (H1), 4 (H4) and 6 (H6) h after the first dose.
- Maximum temperature

Withdrawal of the patient from the study

- Body temperature increases above 104°F or decreased below 96.5 °C
- Occurrence any severe physical event
- Withdrawal of the consent of the parents/guardians.

2. **Tolerability evaluation**

Modified Treatment Tolerability Evaluation Score (MTTES)[7,11]:

Vomiting, dislikeness for meals, daytime sleep and additional medication were assessed and scores were recorded from 0-3 (absent –severe):

Score 0: **Absent -** Symptom is not present

Score1: **Mild -** Symptom is present but is not annoying or troublesome

Score 2: **Moderate -** Symptom is frequently troublesome but would not interfere with normal daily activity or sleep

Score 3: **Severe -** Symptom is sufficiently troublesome to interfere with normal daily activity or sleep

Symptoms for MTTES: Vomiting, Dislikeness for meals, Daytime sleeping, Additional medication

The primary efficacy and tolerability end points were recorded as changes from the baseline values:

Sample size: 62 patients were included in each group according to inclusion and exclusion criteria. (Total sample size: 124 pediatric patients with fever)

Study period: 2 months starting from the date of approval of the study by the Institutional Ethical Committee

Statistical analysis: The data will be collected, pooled, subjected to appropriate statistical analysis and conclusions were drawn

RESULTS AND OBSERVATIONS

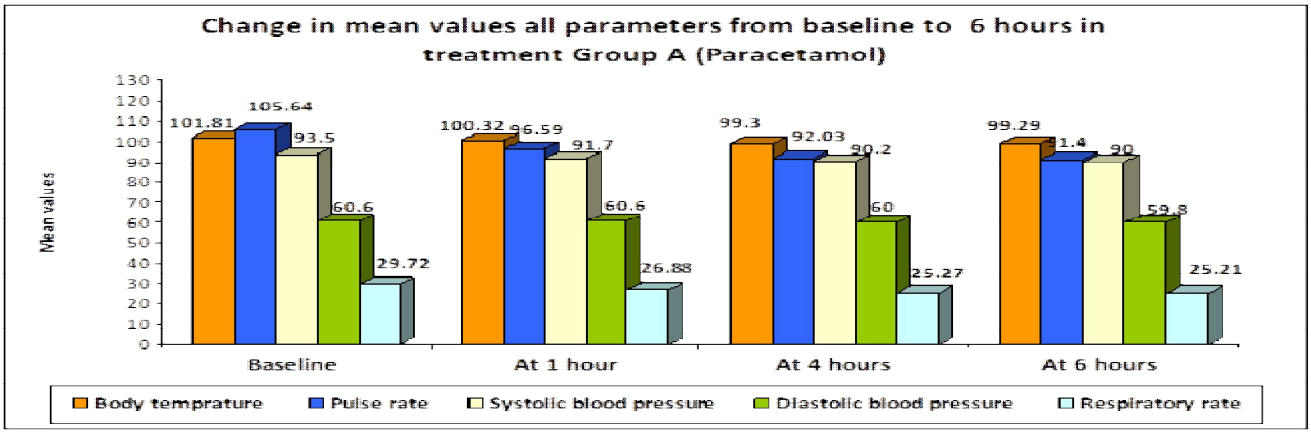

Fig:1. The change in mean values of all parameters from baseline to 6 hours during treatment of patients included in group A (Paracetamol)

By applying Student's Paired 't' test there is a highly significant decrease of body temperature in treatment group A (Paracetamol) from baseline to 1 hour, 4 hours and 6 hours, 1 hour to 4 hours and 6 hours, (i.e. $p<0.01$) and rest all other parameters remained constant at 4 and 6 hours

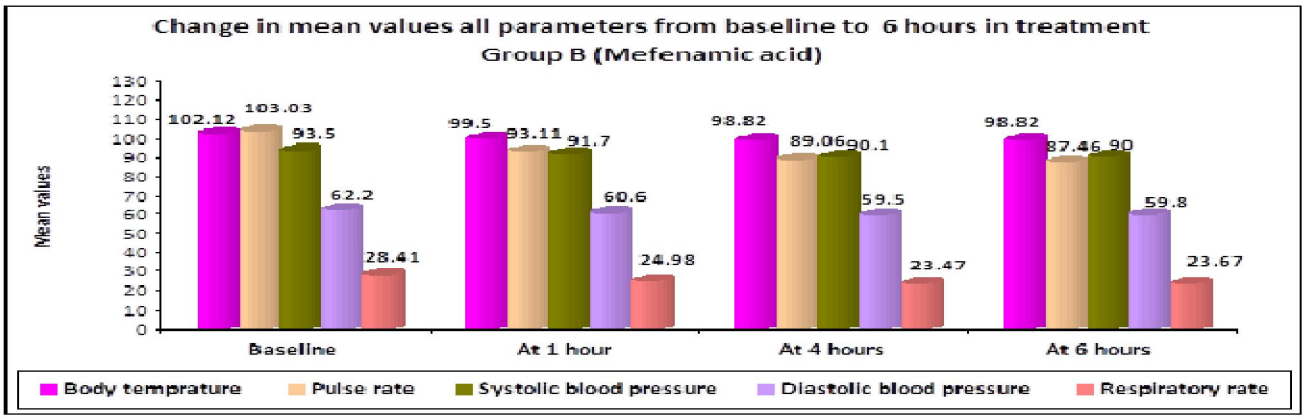

Fig:2. Change in mean values of all parameters from baseline to 6 hours during treatment of group B (Mefenamic acid)

By applying Student's Paired 't' test there is a highly significant decrease of body temperature in treatment group B (Mefenamic acid) from baseline to 1 hour, 4 hours and 6 hours, 1 hour to 4 hours and 6 hours, (i.e. $p<0.01$) and rest all other parameters remained constant at 4 and 6 hours

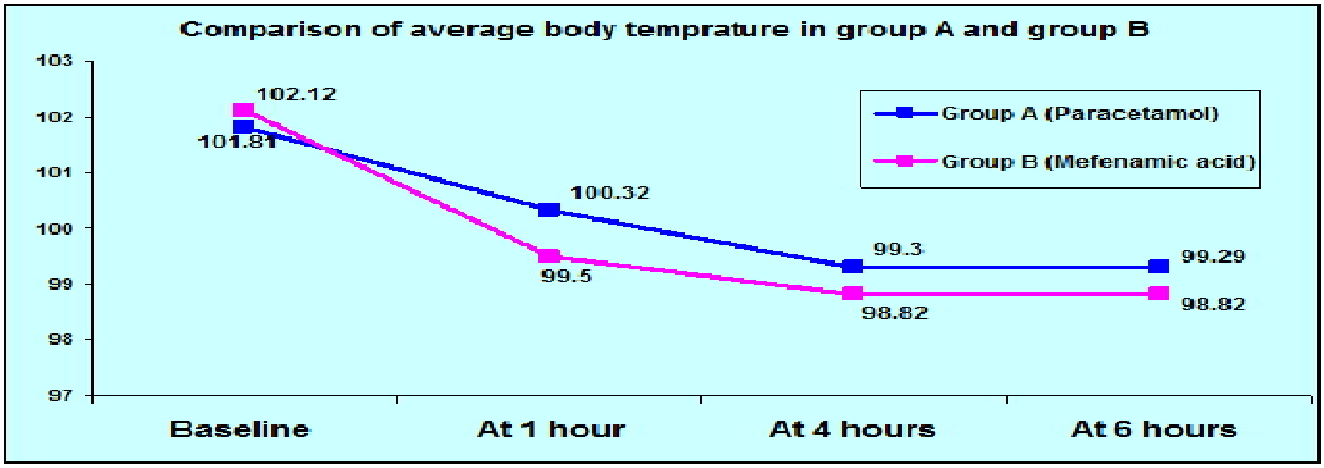

Fig: 3. Comparison of average body temperature in group A and group B

On comparison of average fall in body temperature in group A and group B after applying "Z" test of significance there was a highly significant difference in fall in temperature in Group B from baseline to 1 hour than Group A. Both the groups showed a highly significant fall in temperature from baseline to 6 hours.

Table:1. Distribution of average percentage fall (decrease) from baseline to 6 hours for all parameters in Group A (Paracetamol) and Group B (Mefenamic acid) (n=62)

Parameters	Percentage (%) of fall (decrease) from baseline to 6 hours	
	Group A (Paracetamol)	Group B (Mefenamic acid)
Body temperature (ºC)	2.47%	3.23%
Pulse rate(per min)	13.48%	15.11%
Systolic Blood Pressure (mm of Hg)	3.74%	3.94%
Diastolic Blood Pressure (mm of Hg)	1.32%	3.86%
Respiratory rate (per min)	15.17%	16.94%

It is seen from the above table that the average fall (decrease) all parameters are significantly more in group B as compared to group A, thus it is concluded that drug Mefenamic acid is more efficient / consistent than drug paracetamol in pediatric patients with fever. That is Mefenamic acid shows better and faster recovery of fever in pediatric patients as compared to Paracetamol.

Table:2. Total number of patients suffered with following adverse effect

Group	Vomiting	Dislikeness meal	Daytime sleeping	Additional medication
Paracetamol(n=50)	3	5	5	2
Mefenamic acid(n=50)	2	7	4	2
Significance	P>0.05*	P>0.05*	P>0.05*	P>0.05*

* No significant difference between mean values of MTTES scores between Paracetamol and Mefenamic acid group.

DISCUSSION

The management of children with fever is based primarily on the elucidation and treatment of the underlying cause. The role of antipyretic therapy in such children is aimed at reducing the ever present risk of a febrile convulsion. A variety of pharmacological agents are available for Antipyresis. The so called superiority of one drug over the other is marginal and has no therapeutic significance.[3, 12]In our study both Paracetamol and Mefenamic acid proved to be effective antipyretic drugs. Antipyresis was achieved within 6 hours of administration of the dose. In Paracetamol group the baseline body temperature decreased since 101.81 ° to 99.29 °Fat 6hours while in Mefenamic acid group from 102.12 ° to 98.82 °Fat 6hours. Both the drugs are NSAIDs and act by inhibiting COX enzyme responsible for generating Prostaglandins (PGE2). Paracetamol has only central action with weak anti-inflammatory effect and so has been reported to be the best antipyretic drug. Mefenamic acid has central and peripheral action with anti-inflammatory effect. The fall in temperature at 1 hr was more in Mefenamic acid group (102.12^{o}F to99.5^{o}F)compared with paracetamol group (101.81^{o}F to 100.32^{o}F).These results show that Mefenamic acid has better antipyresis at 1 hour than Mefenamic acid. A rough correlation has been established between the anti synthetase activities of many nonsteroidal anti-inflammatory drugs[13] including Mefenamic acid in central nervous system. Our results are in accord with S. Keininen etal which also states Mefenamic acid to be more potent and powerful antipyretic drug.[8.] The children showed no adverse symptoms or signs in connection with the antipyretic therapy. There was no significant difference on Heart rate, BP and respiratory rate despite a slight fall in all above was noted.

Mefenamic Acid shows highly significant decreases in the body temperature baseline to 6th hour as compared to Paracetamol in paediatric patients with fever (i.e. P<0.01.) This may be due to decline in the efficacy of Paracetamol which has been described as the best antipyretic. It is essential to establish a cause for a fever and then provide effective modern treatment.

A persistent fever is a stimulus to both doctor and parents to maintain their vigilance. The use of the drugs should not become the refuge of the diagnostically destitute. Judicious use of the antipyretics needs to be considered giving due respect to the body's response to the infection in the form of fever[9]. PCM has always been a dependable antipyretic and has an additional advantage of being a cheaper medicine and relatively safer antipyretic. Other drugs like Mefenamic acid have marginally better antipyresis. [1]Study demands more detailed evaluation of the decline in paracetamol efficacy.

CONCLUSION

It is clear from this study that Mefenamic Acid is the best antipyretic as in-terms of their efficacy and tolerability in pediatric patients with fever and can be very helpful in treating febrile illness in pediatric age group more effectively. Mefenamic acid could be a suitable alternative as a "second-line" antipyretic agent, even in selected children. However, more clinical experience and information about side-effects are needed before they can be recommended for wider routine use.

Our study results showed Mefenamic acid to be more efficacious than Paracetamol as antipyretic in the Paediatric age group but more extensive studies and clinical experience is required for its recommendation for wider use as antipyretic. 2. These extensive studies should address safety as well as efficacy issues and should be compared using all possible methods. 3. More extensive studies may yield a better antipyretic alternative to Paracetamol and will also discourage injudicious use of antipyretic drugs like Nimesulide which is banned but still used by some pediatricians. 4. Genetic studies to evaluate the decline in the

efficacy of paracetamol as antipyretic should be taken up.

ACKNOWLEDGEMENT

We acknowledge all the faculty members of the Department of Paediatrics for their help and cooperation for this study

REFERENCES

1. Jagdish Chandra and Shishir Kumar Bhatnagarr. Antipyretics in Children. Indian J Pediatr. 2002; 69 (1) : 69-74
2. Avtar Let al. Antipyretic Effects of Nimesulide, Paracetamol and Ibuprofen-Paracetamol. Indian Journal of Paediatrics. 2000; 67 (12): 865
3. Alexander KC et al. Fever in childhood. Canadian Family Physician.1992; 38: 1832-36
4. K. Rajeshwari. Antipyretic Therapy**.** Indian Pediatrics. 1997; 34 : 409-411
5. B S David. Fever panic. Sri Lanka Journal of Child Health, 2000; 29: 97
6. S Balasubramanian, A Sumanth. Mefenamic acid – Role as Antipyretic. Indian paediatrics. 2010; 47: 453
7. Autret E et al. Evaluation of Ibuprofen versus aspirin and paracetamol on efficacy and comfort in children with fever. Eur J Clin Pharmacol. 1997 ; 51: 367-371
8. S. Keininen et al. Oral Antipyretic Therapy: Evaluation of the N-Aryl-Anthranilic Acid Derivatives Mefenamic Acid, Tolfenamic Acid and Flufenamic Acid. Europ. J. Clin, Pharmacol. 1978; 13: 331-344
9. RP Khubchandani, KN Ghatikar, SS Keny, NG Usgaonkar. Choice of antipyretic in children. J. Assoc Physicians India.1995; 43 (9): 614-6
10. Keith R. Powell. Fever (ch.170). Nelson Textbook of Paediatrics: 16thedition.p738.
11. Bikas Medhi et al. Efficacy of fexofenadine in the Indian population suffering from allergic rhinitis and urticarial. JK Science. 2006; 8: 83 - 85.
12. John hunter. Study of antipyretic therapy in current use. Archives of Disease in Childhood.1973; 48: 313. -314
13. Praveen Kumar Goyal et al. Double blind randomized comparative evaluation of Nimesulide and Paracetamol as antipyretics. Indian paediatrics. 1998 ; 35: 24-26