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Ref.: 1. Tripathi S, Kasture PN. Indian Journal of Clinical Practice. July 2021; 32 (2): 115-123 2. Liu Z, et al. J Brain & Development. 2020; 42: 336 -341
* Above 6 months # Above 40 kg body weight **IL-1β**: Interleukin 1 beta **NLRP-3**: NOD-like Receptor Protein 3

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Pyrogenic Cytokines Mediated Pathophysiology of Fever and Role of Mefenamic Acid in Pediatric Practice

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ABSTRACT

While fever in most cases represents a normal physiological response to illness, many times it is a presenting sign of a more serious underlying condition. Hence, it is important to assess a child who may be suffering with a serious condition and may require treatment in terms of antipyretic agents. The use of antipyretic agents is usually guided by the degree of fever, and the discomfort caused by fever and associated pain. Paracetamol and, more recently, ibuprofen are the generally used over-the-counter drugs for antipyresis. However, of late, there is a trend of increased use of mefenamic acid as antipyretic. Mefenamic acid has shown better efficacy and tolerability as compared to the other nonsteroidal anti-inflammatory drugs (NSAIDs) in use. In this review, authors have assessed the existing literature on the role of mefenamic acid in pediatric fever. They have highlighted the role of mefenamic acid in pediatric febrile illness in terms of clinical uses, efficacy, comparison with other NSAIDs and its safety in pediatric patients. Its probable action in inflammatory fever and febrile seizure due to its inhibitory action on the NLRP3 inflammasome and potential antiviral actions in viral infections are also highlighted, respectively.

Keywords: Pediatric fever, febrile illness, anti-inflammatory, antipyretic, mefenamic acid, fenamates

Fever is one of the most common reasons for visits to doctor in children, contributing to 15-25% of primary care and emergency consultations.[1-3] It is defined as, "a physiologic response characterized by an elevation of body temperature above normal daily variation."[1] Pediatricians frequently prescribe mefenamic acid as an antipyretic and anti-inflammatory drug. It is a nonsteroidal anti-inflammatory drug (NSAID) with antipyretic, analgesic and anti-inflammatory activity which is reported to be highly effective in reducing fever.[4]

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The evidence that NLRP3 inflammasome has a role in the pathophysiology of febrile seizures and mefenamic acid can inhibit this NLRP3 inflammasome, meaning it probably can alleviate the levels of pro-inflammatory cytokines responsible for febrile seizure.[5]

In this article, the authors have explored the evidence available on mefenamic acid, enumerate its role and significance, clinical safety and efficacy in pediatric febrile illness. The role of mefenamic acid as an antiviral agent in febrile illness of viral origin is also highlighted.

METHODOLOGY

To locate evidence on mefenamic acid, the authors conducted a literature search on medical database including PubMed and Google Scholar. The MESH terms used in the search were **((“Mefenamic Acid” [Mesh]) AND “Anti-Inflammatory Agents, Nonsteroidal” [Pharmacological Action]) AND “Fever of Unknown Origin” [Mesh] AND “Fever” AND “Pyrexia” [Mesh]**. The search duration was June 2010 to June 2021. The inclusion criterion of the articles was all articles in English language, articles mentioning the use of mefenamic acid in treating febrile illness. The articles that were excluded from the search were the articles in

any language other than English. The types of articles searched for the present study were clinical trials, systematic reviews and meta-analyses, case reports, case series and narrative reviews.

The abstracts of the searched articles were scanned, and then final articles were identified and selected. Using a backward chronological search method, other relevant articles from the selected articles were also searched and selected if found relevant to the objectives of the present review. Owing to the heterogeneity of the articles available and the time gap between them, a narrative review was developed based on themes that were identified as a result of analysis of the selected articles.

RESULTS AND DISCUSSION

Based on the search methodology, 46 articles were selected. The themes that emerged as a result of the analysis of the selected literature included information on fever, pathophysiology, assessment, treatment of fever, use of antipyretics and the place and value of mefenamic acid in treatment strategy of pediatric febrile illness.

Fever

Fever is the most frequent reason for visit to the doctor in pediatric clinical practice and emergency department.[6] Fever is an abnormal rise in the body temperature occurring as a result of a biologic response managed and controlled by the central nervous system (CNS). It is dependent on the age of the child and the clinical circumstances.[7-10] Fever is a controlled physiologic phenomenon, owing to protective mechanisms in the thermoregulatory centers; however, adverse events after a febrile illness are many times related to neural immaturity and the underlying disease.[1] Table 1 depicts the temperature elevation that is considered abnormal in children.

The most common causes of fever in children are:[1,6]

- Infections
- Noninfectious causes – immune-mediated, inflammatory and neoplastic conditions
- Fever of unknown origin – cannot be identified by history and physical examination.

Thermoregulation

Current evidence suggests that the core body temperature is controlled by several independent thermoeffector loops with their own efferent and afferent shoots. This led to the conclusion that the regulation of body temperature is dependent on a thermoregulatory circuitry. The anterior hypothalamus is the major thermoregulatory center in the CNS, where both the peripherally and centrally generated temperature signals converge and diverge. Heat sensitive neurons form the preoptic regions which are stimulated or blocked in response to the alterations in temperature. A sensitive balance between heat loss and heat gain regulates the body temperature to optimum limits. An early rapid phase (peripheral prostaglandin E2 [PGE2]-dependent) and a delayed late phase (central PGE2) mark the febrile response. As a result, while peripheral PGE2 may act to initiate the febrile response, central PGE2 may be mostly involved in its maintenance.[11]

The second humoral pathway is directed by circulating pyrogenic cytokines (IL-1β, IL-6, tumor necrosis factor [TNF]-α). They send fever indicators to the thermoregulatory network through indirect and direct routes. The indirect pathway includes the binding of cytokines outside the brain and stimulating the cytokine receptors located on capillaries of the circumventricular organ resulting in PGE2 release. The direct pathway involves disruption of the blood-brain barrier by the circulating cytokines giving direct access to cytokine receptors present on vascular, glial and neuronal structures of the brain. While PGE2 is essential in the febrile response, certain cytokines such as IL-6 may also trigger the febrile response independent of PGE2.[11] In fact, it has been reported that the centrally produced IL-1β may act as a pro-epileptic agent and

Table 1. Fever of Concern as per Age and Clinical Circumstance

Age	Fever of concern	Clinical circumstance
Infant younger than 3 months of age	Rectal temperature ≥38.0°C (100.4°F)	Otherwise, healthy
Children 3-36 months	Rectal temperature ≥39.0°C (102.2°F)	No focus of infection on examination
Older children	Oral temperature ≥39.5°C (103.1°F)	

The temperature thresholds of concern for children with underlying conditions like sickle cell diseases, neutropenia are different.

Table 2. Humoral and Neural Pathways of Fever

	Humoral pathway	Neural pathway
Fever signals	Carried by pathogen-associated molecular patterns (PAMPs) and pyrogenic cytokines	Peripheral nerves such as cutaneous sensory nerves and the vagus nerve.
Mechanism	1. Circulating PAMP lead to release of PGE2 from the arachidonic acid pathway. PGE2 diffuses across the blood-brain barrier, binds to specific PGE2 receptors (EP3 receptor) in the preoptic area activating thermal neurons to a higher thermal balance point. Early phase: dependent on PGE2 synthesis Second phase: dependent on centrally synthesized PGE2 Peripheral PGE2 initiate fever, while central PGE2 maintains it.	1. Localized PGE2 synthesized at inflammation sites may activate cold-sensitive cutaneous nerves, transmitting fever signals to the brain.
	2. Second pathway is guided by circulating pyrogenic cytokines as explained earlier.	2. Circulating pyrogens stimulate liver to produce endogenous mediators like pyrogenic cytokines. These cytokines activate the hepatic arm of the vagus nerve within the nucleus of tractus solitarius from where the signal is transmitted to the preoptic and hypothalamic regions through the ventral noradrenergic bundle stimulating release of norepinephrine. Norepinephrine activates the vagal pathway by triggering rise of core body temperature mediated by α_1-adrenoceptor and dependent on PGE2.

hence linked with the development of febrile seizures in children.[12]

Table 2 gives an overview of the humoral and neural pathways of fever.

Pathophysiology of Fever

Fever can be described as a hallmark of infectious and inflammatory diseases.[13] There are three pathophysiologic bases of fever: 1) Fever due to the rise of the hypothalamic set point in the CNS, 2) fever due to heat production exceeding heat loss, and 3) fever caused by defective heat loss. The first type of fever can be reduced with the help of antipyretics and physical removal of the heat.[14] Fever is the result of a physiological process triggered by an external stimulus. Pyrogens are substances which may be infectious microorganisms, toxins released by microorganisms or pyrogenic cytokines that prompt fever.[15]

Exogenous Pyrogens

Infectious microorganisms such as bacteria, virus, fungi or toxins are exogenous pyrogens (ExP) that incite fever, often within 2 hours of exposure. The ExP interact with macrophages or monocytes triggering the cytokine induction. Several other mechanisms may also be involved in the development of fever, including: (a) Bacterial endotoxins, acting directly on the hypothalamus to change the set point; (b) Lymphocyte activation by ExP; (c) Release of IL-1 via release of lymphokines activated by bacterial endotoxins. Some pyrogens are nonmicrobial in nature such as antigen-antibody complexes, steroids, some hormones, drugs and intracranial lesions such as bleeding and thrombosis. In blood transfusion reactions and immune hemolytic anemia, phagocytosis is the main mechanism behind causing fever.[15]

Endogenous Pyrogens

Exogenous pyrogens including microbial pyrogens-bacteria, virus, and fungi and nonmicrobial pyrogens start the cycle by stimulating host cells, especially macrophages, to produce and release endogenous pyrogens like IL-1. Endogenous pyrogens trigger the synthesis of prostaglandins (PGE2) via the mediation of CNS, which raise the thermostatic set point to initiate the febrile response. PGE2 is the most important prostaglandin involved in the heat production. IL-1 also activates T-lymphocytes to produce various factors, such as INF and IL-2, important for immune response.[15]

The major fever causing cytokines are IL-1β, IL-1α, IL-6, TNF-α and INF-α. These cytokines can be produced in the periphery and brain and have pyrogenic effect directly affecting the production of PGE2 from the hypothalamus which resets the thermoregulatory set point. As a management approach, if the pyrogenic cytokines disappear from the circulating blood or cyclooxygenase (COX) is inhibited, the hypothalamus is again reset downward, thereby triggering the heat dissipation process and temperature reduction via vasodilation and sweating. NSAIDs such as mefenamic acid can lower the cytokines from circulation, thereby reducing fever.[16]

ROLE OF ANTIPYRETICS IN MANAGING FEVER

Not only is fever one of the most troublesome symptoms for parents and caregivers as well as healthcare providers, but it also raises the concern that if untreated, it may progress to brain damage, seizures and death, even though there are no definitive evidence to prove this. Fever management differs in specific clinical situations. Fever may increase metabolic and oxygen consumption; hence, aggressive treatment may sometimes be needed.[1]

In a febrile illness, discomfort is usually due to an associated pain, such as myalgia, a sore throat or a headache. Antipyretic medications are required to improve comfort, along with improvements in eating, feeling of irritability, and providing pain relief and reduce chances of dehydration.[17] Besides, parents have also reported issues in giving medicines to a sick child. In a survey, it was reported that 85% of parents has to wake their children to give antipyretics.[18]

In a clinical report from the American Academy of Pediatrics, it has been suggested that the primary aim of offering treatment for a febrile child should be to improve the wholesome comfort level of the child and not just reduce the temperature.[19] A long-acting antipyretic will offer a long-lasting reduction of body temperature and provide the necessary comfort. Physical treatments like tepid sponging or cold baths are not recommended due to modest efficacy.[1]

Majority of healthcare workers believe that the risk of heat-related adverse outcomes is increased with temperature above 40°C (104°F) and almost 90% of health practitioners prescribe antipyretic therapy at temperatures >39°C.[20,21] In a large UK pediatric study in ICU patients, it was shown that the threshold for treatment of fever is still 38°C and 58% of caregivers in the study reported a fever of 39°C to be unacceptable.[22]

Febrile seizures is the most common type of acute seizure, affecting approximately 2-14% of children aged 6 months to 5 years worldwide. The pro-inflammatory cytokines viz. IL-1β, IL-6, TNF-α have been implicated in fever with IL-1β as central to initiation and regulation of inflammation which is released by activation of NLRP3 inflammasome. A significant increase of NLRP3 inflammasome expression is evident in children with febrile seizure as compared to controls.[23] The most commonly used antipyretics are NSAIDs with significant analgesic effect, thus promoting the feeling of well-being. There is a lot of variance among pediatricians prescribing antipyretic medicines for children.[16]

Presently, paracetamol, mefenamic acid and ibuprofen are the antipyretics of choice used to treat fever in kids.[24] Among individuals with normal renal function with no other risk factors, such as dehydration, for an acute renal hemodynamic effect, there is no risk associated with the use of NSAIDs.[25]

Adverse Events Associated with Antipyretics

Paracetamol can be prescribed to infants from birth. However, paracetamol has a narrow therapeutic index and infants and children are at increased risk of overdose. Children aged under 5 years who are acutely unwell are particularly vulnerable to paracetamol toxicity, which can lead to liver failure and death.[26]

While paracetamol has the ability to reduce fever and pain, it lacks the anti-inflammatory activity that might be fundamental in containing exacerbation of diseases having inflammatory origin. It has been argued that preferential use of paracetamol may lead to an oxidative imbalance, deteriorating the clinical outcomes in a coronavirus disease 2019 (COVID-19) patient.[27]

Paracetamol may also lead to adverse effects in the presence of risk factors, such as dehydration, and in the case of medication errors such as overdosing or too frequent adminsitration.[26,28] Acetaminophen is associated with hepatic injury[29] while ibuprofen is linked with gastrointestinal bleeding and both have an increased risk of asthma in early childhood.[1,30,31]

MEFENAMIC ACID

Role of Mefenamic Acid in Fever

Mefenamic acid exerts central and peripheral actions in prostaglandin inhibition. It also blocks the E-type prostanoid (EP) receptors, thus inhibiting the pre-formed prostaglandins. Hence, it has a prominent action on all the fever producing pathways. Due to its dual action,

it can significantly reduce the inflammatory cytokines thereby improving sleep, and other symptoms such as myalgia and arthralgia associated with fever.[5]

Mefenamic acid exerts its action by blocking the COX enzyme or prostaglandin H synthase (PGHS), thus disrupting the conversion of arachidonic acid to its metabolites, including prostaglandins, prostacyclin and thromboxane. By being a preferential COX-2 selective inhibitor, mefenamic acid not only leads to an antipyretic, anti-inflammatory and analgesic effect, but it improves effectiveness without inducing significant gastrointestinal side-effects.[5]

Clinical studies suggest safe use of mefenamic acid above 6 months at 4-6.5 mg/kg/dose as antipyretic. In general, for children above 6 months the dose suggested is 25 mg/kg/day in three divided dosages.[16,32]

Clinical Evidence

A study compared the ability of mefenamic acid with that of acetylsalicylic acid, paracetamol and aminophenazone, in reducing fever in children. In this study, a series of cases including 71 patients (age 3 months to 15 years with rectal temperature above 38.5°C) were observed and the antipyretic effect of mefenamic acid in a dose of 4 mg/kg was optimum. The effect was reported to be 2.5 times that of paracetamol and at par with that of aminophenazone. The study concluded that the antipyretic effect of mefenamic acid was stronger than its anti-inflammatory and analgesic properties.[33]

In a study comparing the relative efficacy of 3 anti-pyretics-mefenamic acid, ibuprofen and paracetamol, the results showed that mefenamic acid group with 29 patients demonstrated a fall of 3.5°F at the conclusion of 4 hours compared with the paracetamol group (29 patients) that showed a fall of 2.44°F at the end of 4 hours and ibuprofen group (20 patients) showing a fall of 2.79°F. The results of this comparative study have shown that mefenamic acid showed significantly better antipyretic activity compared to paracetamol ($p < 0.05$) over 4 hours and ibuprofen ($p < 0.05$) in the 2- to 4-hour range. In fact, it was suggested that mefenamic acid displayed a persistent activity even at the end of 4 hours compared to paracetamol and ibuprofen.[34]

In another study conducted to compare the antipyretic effect of paracetamol and mefenamic acid in pediatric patients, it was suggested that mefenamic acid has more efficacy and equal tolerability compared with paracetamol as an antipyretic in pediatric patients with fever. The antipyretic efficacy of mefenamic acid was reported to be higher than paracetamol ($p < 0.05$). The researchers have suggested mefenamic acid as the best alternative to paracetamol.[16]

In a randomized, open-label study, it was shown that mefenamic acid has faster onset of action. Its efficacy at the end of 6 hours is maximum as compared to paracetamol and ibuprofen. Mefenamic acid, at the end of 24 hours, demonstrated highest reduction in the baseline mean temperature among the three study groups, including mefenamic acid, paracetamol and ibuprofen groups. The study authors concluded that mefenamic acid is a better antipyretic compared to paracetamol and ibuprofen in terms of faster onset of action and prolonged effect.[24] Besides, it also gives comfort to parents with 'fever phobia'[18] who do not need to disrupt their child's comfort by awakening them from sleeping.

It is an established fact that febrile seizures are the most common convulsions in childhood, which is believed to be activated by IL-1β. In a recent study, it has been reported that NLRP3 protein was considerably increased in children with typical febrile seizure compared to in fever only controls. Increased NLRP3 can mediate the release of IL-1β which is responsible for febrile seizures in children.[23,35]

Mefenamic acid inhibits the NLRP3 inflammasome and the release of IL-1β by blocking the membrane volume regulated anion channel and volume-modulated transient receptor protein channels. It acts independently of its COX-mediated anti-inflammatory activity.[5] The NLRP3 inflammasome inhibitory activity of mefenamic acid can be a promising potential therapy in the prevention and/or management of febrile seizures in children. This further broadens the scope of mefenamic acid use in children with febrile illness.

Mefenamic acid is also approved for use as an anti-inflammatory analgesic for the symptomatic relief of rheumatoid arthritis, osteoarthritis and pain including muscular, traumatic, dental pain and pyrexia in children. It is also used for primary dysmenorrhea in older children and adolescents.[36] Mefenamic acid is one of the prescribed antipyretic medications for the treatment of fever. Mefenamic acid, the potent COX inhibitor, has both central and peripheral action and is recommended to be used in a dose of 4-6.5 mg/kg/dose.[16,36] It is also included in the National Formulary of India for the treatment of rheumatoid arthritis, osteoarthritis, dysmenorrhea, mild to moderate pain, inflammation, fever, and dental pain.[37]

In a study, it was demonstrated that mefenamic acid and doxycycline, when used together, led to significant inhibition of DENV2 NS2B-NS3pro resulting in significant reduction of viral load. In the study, mefenamic acid depicted better selectivity against dengue virus replication *in vitro* compared to doxycycline. Hence, the anti-dengue and anti-inflammatory properties of mefenamic acid can be a promising therapy in the management of dengue.[38]

In another study, mefenamic acid and meclofenamic acid demonstrated significant antiviral activity against viral replication either alone or in combination with another antiviral drug, ribavirin, besides leading to significant reduction of pathological signs. The results of the study led to the possibility of further expansion of the clinical spectrum of mefenamic acid.[39]

Mefenamic Acid vs. Other Antipyretics

Paracetamol has been used as an antipyretic for a long time and it exerts its effect by reducing prostaglandin synthesis in the brain. However, paracetamol does not inhibit the synthesis of prostaglandins in the periphery unlike mefenamic acid.[36] There have been some reports of failure of antipyretic drugs such as paracetamol in controlling fever, giving rise to use of mefenamic acid as an antipyretic. While paracetamol has only central action with weak anti-inflammatory action, mefenamic acid, on the other hand, has central and peripheral action with significant anti-inflammatory effect, with better antipyresis at 1 hour.[16]

Mefenamic acid has demonstrated similar analgesic and anti-inflammatory effect compared with ibuprofen in a study. The study also revealed similar side effect profiles for the two drugs except for drowsiness seen in 6 cases with ibuprofen and 2 cases with mefenamic acid.[40] In a case series and reports, it has been suggested that mefenamic acid may have a beneficial effect in patients with bronchial asthma,[41,42] whereas ibuprofen and paracetamol have been associated with increased risk of asthma.[30,31]As previously mentioned, it has been shown that mefenamic acid has better efficacy and tolerability compared with paracetamol and ibuprofen.[24]

Nimesulide is an NSAID with anti-inflammatory, analgesic and antipyretic properties, with efficacy at par with naproxen, acetylsalicylic acid, mefenamic acid and paracetamol. However, nimesulide may cause fulminant hepatitis. On the other hand, mefenamic acid is an NSAID with dual activity - central as well as peripheral analgesic action.[16] The Government of India as well as many other countries like Switzerland, Spain, and the United States have banned nimesulide for pediatric use in common fever and pain because of its detrimental effects on the liver.[43] Additionally, as shown above, the unique inhibitory action of mefenamic acid on NLRP3 inflammasome may assist in attenuating fever and inflammation effectively.

Pediatric Safety and Efficacy

In a clinical trial including 87 children, mefenamic acid showed optimum fever control at a dose of 4 mg/kg. Its antipyretic activity was reportedly higher than the antirheumatic effects.[44] Mefenamic acid has comparatively better efficacy and tolerability than other NSAIDs (ibuprofen) or paracetamol.[24] The results of a clinical trial have demonstrated that there were no hypersensitivity or intolerance events associated with the use of mefenamic acid. Besides, no side effect from the short-term therapy in children for fever was observed.[45]

The safety of mefenamic acid has been established from the various clinical studies as published. It has been used for closure of symptomatic patent ductus arteriosus in preterm infants (2 mg/kg once in 24 hrs), especially in those patients where intolerance to indomethacin is seen or minute titration of dosage is not possible.[46]

Mefenamic acid is considered to be one of the safest drugs in terms of safety outcome and is registered for use since 6 months of age in children with fever.[17] As per the official journal of the American Academy of Pediatrics, mefenamic acid can be safely used in breastfeeding mothers.[5]

CONCLUSION

Even though there are variances among clinical judgments, many pediatricians routinely prescribe antipyretic agents to treat fever. These antipyretics belong to NSAIDs, with paracetamol, mefenamic acid and ibuprofen being the current choices of drugs. The dual action of mefenamic acid (central and peripheral), and COX enzyme inhibition and blocking of EP receptor, makes it a unique entity in the landscape of fever management. The novel actions (NLRP3 inflammasome inhibition and potential antiviral action) as evident from literature makes it stand out in comparison with other NSAID options. It has a longer duration of antipyretic action and also possesses proven anti-inflammatory and analgesic actions. Many studies have shown that mefenamic acid has better efficacy as an antipyretic

agent compared to paracetamol in pediatric patients. The comparable safety profile of mefenamic acid is also superior to other drugs in the same category used for treating fever.

However, the authors would like to state that more extensive studies comparing the efficacies, safety and multifactorial use of NSAIDs as an antipyretic, anti-inflammatory and analgesic agent must be conducted in pediatric patients for an informed clinical decision on their utility in children with febrile illness. Future clinical studies to explore the role of mefenamic acid in conditions of febrile seizures or febrile infection-related epilepsy syndrome (FIRES) are also recommended.

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