Personal Practice

Antipyretic Therapy

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Fever is among the most common manifestations of disease and antipyresis is one of the most usual therapeutic intervention undertaken. A variety of microbial products including endotoxins and exotoxins are recognized as exogenous pyrogens which induce host cells to produce mediators known as endogenous pyrogens. The best studied endogenous pyrogen is interleukin 1, others include tumor necrosis factor and interferons(l). Most known endogenous pyrogens act on the anterior hypothalamus to elicit local generation of prostaglandins. Fever represents the response of the host to a neurologic signal demanding thermal upregulation. Studies have shown temperature elevation to enhance several parameters of immune function like T cell activation, mononuclear production of leukocyte migration inhibition factor, neutrophil function and macrophage oxidative metabolism(2,3) while high temperatures prove deleterious by altering natural killer cell activity, generation of cytotoxic T lymphocytes and alteration in neutrophil morphology and function(4). While the clinical situation is much too complex to allow definite conclusions, the preponderance of evidence suggests that temperatures in the range of usual fever may render many host defenses *noro active andmany pathogens more susceptible to there defenses more active and many pathogens more susceptible to these defenses. Thus the limited data that exist do support the hypothesis that fever has some beneficial effects in human infection. This communication addresses the need and available modalities for antipyresis in pediatric practice.

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Is Antipyresis Required?

A common stated reason for aggressive antipyretic therapy is the prevention of febrile seizures or other central nervous system effects. Although the height of fever is considered important in seizure induction^), it is not clear whether aggressive antipyresis alters the risk of an initial febrile seizure. Epilepsy may manifest during febrile episodes. Fever may precipitate status epilepticus in some children and further result in motor incoordination and other disabilities(6). Most physicians can recall instances of transient delirium in febrile patients but it is difficult to determine whether the reversible manifestation arises from the fever or from the disease producing the fever(7). It is yet not scientifically proved whether antipyretic therapy can prevent or reverse delirium in identifiable high risk situations or minimize risk of status epilepticus.

Another common reason for antipyretic therapy is symptomatic treatment of fever. It is less clear exactly what symptoms are being treated and to what extent antipyresis actually makes the patient feel better. Conversely, there is a possibility that a febrile patient given antipyretics may become abruptly afebrile or even hypother-

mic with profuse diaphoresis and greater discomfort than if untreated(8). In treating fever symptomatically one should not lose sight of the fact that elevated temperature whatever their physiologic function do serve as a signal both to the patient and to the caregiver. Non specific suppression of fever may deprive one of clues to a need for further diagnostic investigation or for changes in therapy.

In the light of available scientific data, the decision for antipyresis is usually based on the "perceived" risk and benefits, both of the fever itself and of the available treatments. The definition of dangerous hyperpyrexia requiring treatment is clearcut and supported by clinical data. A rectal temperature above 41.4°C is definitely harmful and requires therapy(9). In other patients, a cited reason for trying to suppress fever is concern about hypoxic injury to tissues, especially the cardiovascular system. Metabolic rate and tissue oxygen demand increase with elevated body temperature. Cardiac compromise has been reported at extreme hyperthermic temperatures. Similarly, subclinical compromise of cardiac function has been documented during febrile illnesses. Thus patients with severe valvular heart disease with precarious coronary perfusion may benefit from prompt antipyresis to prevent worsening of clinical condition.

In addition to the antipyretic effect, most commonly used antipyretics particularly Non Steroidal Anti Inflammatory Drugs (NSAIDS), have considerable analgesic effect which promotes a general feeling of well being for the duration of effect. In the usual clinical setting, antipyresis is generally resorted to for promotion of this feeling of "well being" as well as for reduction of fever, often to allay anxiety and reassure the patient and relatives. In this context, the effect (beneficial or otherwise) of antipyretics on the biological process is as yet not clear.

Physical Antipyresis

Physical modalities such as sponging, ice packs or cooling blankets are most often used in conjunction with pharmacological antipyresis. It has been shown that use of iced water or alcohol in water is superior to sponging with tepid water though associated with more patient discomfort(lO). External cooling by sponging in a bath tub with 5-10 cm of tepid water increases evaporation and promotes heat loss. Cold water should be avoided because it results in peripheral vasoconstriction and shivering, causes greater discomfort to the child and may also increase the core body temperature(10,11). Sponging for 20 minutes was found to be ineffective(12) and sponging for 2-4 hours has been recommended(13). Wet compresses covering the lower legs or trunk are frequently used to lower the body temperature. Usually they are changed after 10-15 minutes and repeated till the skin feels cool. No controlled trials proving their efficacy are available.

There is a fundamental illogic to the use of external application of cold to lower body temperature in a patient with true fever. Because of the altered hypothalamic set point, the patient is already responding as if to a cold environment. Physical methods should only be used after administration of antipyretic drugs, so that the hypothalamic set point is lowered from its febrile values. Even in this setting, their utility in the reduction of fever can be debated. One study found that sponging febrile children with tepid water after antipyretic therapy had no more effect on defervescence than antipyretics alone(12). Thus physical methods may be used only if there is failure of pharmacotherapy or when temperature is to be lowered for a reason not associated with true fever (heat stroke, or

induction of profound hypothermia in head trauma or cardiac surgery)(13)

Pharmacological Antipyresis

Antipyresis occurs with differsnt classes of substance including steroids, acetylsalicylic acid, dipyrone, acetaminophen and the non steroidal anti-inflammatory agents represented by indomethacin, mefenamic acid, ibuprofen and the latest nimesulide. Some antipyretics are anti-inflammatory, some are not while most have pronounced analgesic properties. The decision to choose an antipyretic should be dictated by efficacy, safety, duration of effect and cost.

One of the oldest antipyretics in use is *acetyl salicylic acid* (ASA). The mode of action of ASA is not wholly understood. It inhibits cyclo-oxygenase which catalyses the conversion of arachidonic acid to prostaglandin E2. This reduction of prostaglandin E2 in the brain is believed to lower the hypothalamic set point. Since ASA also possesses anti-inflammatory activity, this is beneficial in patient with inflammatory processes. Both the absolute (reduction of initial temperature) and relative (in comparison to paracetamol or other drugs) antipyretic efficacy of ASA in febrile children have been extensively evaluated(14-18). Compared to paracetamol, ASA has equal antipyretic efficacy. Differences in the onset and duration of action may exist for different doses, but similar doses of each drug produced a similar time of onset (0.6-0.9 hours) and duration of action (at least 3 hours)(15). Adverse effects of ASA after a single dose (hepatotoxicity) are also known. Use of salicylates has demonstrated a strong statistical association with Reye syndrome; patients with Reye syndrome were found to have significantly higher total and average daily doses of salicylates than matched controls(19). The easy availability of ASA increases the chance of toxicity. Further, at therapeutic plasma levels, ASA affects blood coagulation. Hence because of availability of equally potent and safer drugs, ASA is currently not recommended as a first line antipyretic.

Another antipyretic in use for a considerable time is *acetaminophen (paracetamol)*. 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 effects. *Ibuprofen* belongs to the propionic acid group of NSAIDS. The antipyretic effects of paracetamol and ibuprofen have been compared in various studies(20-26). The largest double blind acetaminophen controlled trial has established the safety of ibuprofen for antipyresis in children. It involved 84192 children and proved that the risk of gastrointestinal bleeding, renal failure or anaphylaxis was not increased following short term use of ibuprofen(23). Some of these studies have also shown a longer duration of action for ibuprofen (8 hours) *vis-a-vis* acetaminophen(20,22). In a dose of 10 mg/kg, ibuprofen suspension, and *possibly* 5 mg/kg ibuprofen, produce equally tolerated, greater and longer lasting fever control than 10 mg/kg paracetamol elixir, especially in children with oral temperatures above 100.5°F(20). While further confirmatory evidence is awaited, ibuprofen liquid (10 mg/kg) and paracetamol (15 mg/kg) administered every 6 hours for 24 to 48 hours appeared to be most effective in reducing fever. Lower ibuprofen doses (2.5 mg/kg and 5 mg/kg) were less effective than paracetamol and 10 mg/kg ibuprofen(24). When administered every 6 hourly, there was no significant difference between 10 mg/kg ibuprofen therapy and 15 mg/kg paracetamol. *Thus used in these doses, the*

above drugs are equally efficacious. Dose dependent efficacy has also been found for 5,10 and 20 mg/kg paracetamol but the duration of action differed in the trials performed^). More data are required from prospective comparative trials together with the recently adjusted higher dose and shorter dosage intervals of acetaminophen.

There is only one study comparing the antipyretic efficacy of ibuprofen and paracetamol in children wijih febrile seizures(28). Other studies in children without febrile seizures have demonstrated significantly lower temperatures at 3-5 hours after initial dose of ibuprofen(29,30). Clinicians usually pursue rapid fever reduction in children with febrile seizures. In this respect a 0.5°C greater temperature reduction at 4 hours was documented with ibuprofen. Few recurrent seizures occurred in this study and seizure prophylaxis was not evaluated. No placebo controlled groups were used. A large placebo controlled trial is necessary to determine whether antipyretics, especially ibuprofen can prevent febrile seizure recurrences.

Dipyrone (Metamizol), a pyrazolone, is also effective as an antipyretic. However, the mechanism by which dipyrone exerts its antipyretic effect is still unclear. It probably has a direct action on the central nervous system and possibly an additional peripheral inhibition of endogenous pyrogen synthesis and release. Double blind clinical trials on dipyrone are not available. The antipyretic effect of this drug was compared with paracetamol in a single blind controlled trial(31). Dipyrone in dose range of 13.2 to 22.3 mg/kg was superior to paracetamol (dose range 13.2-22.3 mg/kg) 1.5 hours to 6 hours after drug intake. The only reported adverse effect of this drug is agranulocytosis, the risk of which is approximately 1 per million per week of treatment(32). However, because of controversy raised over this, dipyrone is not marketed in several countries. Most of the reports dealing with the risk of agranulocytosis were based on observations of small numbers of cases and matched controls(33,34). Additional graded dose comparative trials with dipyrone should be carried out in order to determine the optimum dose for treating febrile children.

The latest drug *Nimesulide* (4-nitro-2-phenoxymethane sulfonanilide) is a non steroidal anti-inflammatory drug with analgesic and antipyretic properties. Its efficacy has been compared with naproxen, ASA, paracetamol and mefenamic acid(35-38). Though these demonstrated the superior efficacy of nimesulide, these studies were not double blinded and comprised small groups of children. More controlled data is necessary before drawing any firm conclusions. However, this drug may offer a theoretical advantage of reduced frequency in dosing (8-12 hourly).

Corticosteroids are also highly effective antipyretics. Although they have a place in the treatment of certain infections wherein the effects of inflammation may be devastating, their adverse effects on host defenses and risk of bowel perforation in inflammatory states have prevented them from being used for antipyresis *per* se(39,40).

Table I summarizes the available pharmacological antipyretics with their age wise recommended doses and frequency of administration(37,41-43).

Recent data indicates that factors other than the type of antipyretic agent employed are also important determinants of the response to therapy. Multivariate analysis indicates that pharmacokinetics of ibuprofen and perhaps all antipyretics are determined by age and initial temperature(43). Thus if studies are conducted age wise, using different doses of antipyretic

TABLE I—Dose *and Frequency of Administration of Commonly Used Antipyretics*

Drug	Dose	Frequency of administration	Remarks
Ibuprofen(43)	10 mg/kg/dose	6-8 hourly	Age wise dose not stated
Nimesulide(37)	1.5 mg/kg/dose	8-12 hourly	Age wise dose not stated
Acetyl salicylic acid(42)	30-65 mg/kg/ 24 hours	4-6 hourly	Not recommended as first line antipyretic
Paracetamol(41)			
2-3 years	10 mg/kg/dose	4-6 hourly	Perhaps the safest antipyretic
4-5 years	12-15 mg/kg/dose	4-6 hourly	
6-8 years	15-20 mg/kg/dose	4-6 hourly	

drugs over various temperature ranges, clear cut differences may emerge regarding their efficacy.

Fixed Dose Antipyretic Drug Combinations

Such combinations are commercially available and are being aggressively promoted by some pharmaceutical companies. Unfortunately, there is no concrete scientific data in the form of randomized controlled trials to guide the clinician regarding the utility or otherwise of such fixed dose antipyretic drug combinations. Theoretically, a combination of two antipyretic drugs may be expected to result in a greater antipyresis, analgesia and feeling of "well being". However, this could also result in more risks of adverse effects. Further, the doses of antipyretics vary at different ages (especially paracetamol) and formulation of optimal drug combinations over the entire age range seems impossible. It would therefore be prudent to avoid fixed dose antipyretic drug combinations until concrete scientific evidence to the contrary is available.

Concluding Comment

Prompt physical antipyresis is indicated when temperature is to be lowered for a reason not associated with true fever (heat stroke, or induction of profound hypothermia **in** head trauma or cardiac surgery). Further, antipyretic therapy is warranted for dangerous hyperpyrexia (rectal temperature >41.1°C) and fever in subjects with precarious coronary perfusion (severe valvular heart disease). In the vast majority of febrile infectious illnesses, there is no concrete evidence that fever is detrimental or that antipyretic therapy offers any significant benefit. Despite this, in the actual clinical setting, antipyretic agents are invariably prescribed for a combination of antipyresis, analgesia and general feeling of "well being".

A variety of pharmocologic agents are available for antipyresis. The so called superiority of one drug over the other is marginal and has no therapeutic significance. Given in appropriate doses, ibuprofen and paracetamol are equally efficacious and safe. Pending the availability of firm scientific evidence, it would be prudent to avoid fixed dose antipyretic drug combinations.

REFERENCES

1. Endres S, Van der Meer JWM, Dinarallo CA. Interleukin-1 in the pathogenesis of fever. Eur J Clin Invest 1987; 17: 467-474.
2. Jampel HD, Duff GW, Gershon RK, Atkins E, Durum SK. Fever and immuno

regulation III: Fever augments the primary *in vitro* humoral immune response. J Exp Med 1983; 157:1229-1238.

3. Roberts NJ, Sandberg K. Hyperthermia and human leukocyte migration inhibition factor (LIF). J Immun 1979; 122:1990-1993.

4. Azocar J, Yunis EJ, Essex M. Sensitivity of human natural killer cells to hyperthermia. Lancet 1982; 1:16-17.

5. Millichap JG. Studies in febrile seizures: Height of body temperature-A measure of the febrile seizure threshold. Pediatrics 1959; 23: 76-85.

6. Fishman MA. Febrile seizures: Treatment controversy. J Pediatr 1979, 94: 177-184.

7. Lipowski ZJ. Delirium (acute confusional states). JAMA 1987, 258:1789-1792.

8. Done AK. Treatment of fever in 1982: A review. Am J Med 1983; 74 (Suppl): 27-35.

9. Schmitt BD. Fever in childhood. Pediatrics 1984; 74 (Suppl): 929-936.

10. Steel RW, Tanaka PT, Lara RP, Bass JW. Evaluation of sponging and of oral antipyretic therapy to reduce fever. J Pediatr 1970; *77:* 824-825.

11. Aynsley GA, Pickerning D. Tepid spong ing in pyrexia. Br Med J 1975; 2: 393-394.

12. Newman J. Evaluation of sponging to reduce body temperature in febrile children. Can Med Assoc J 1985; 132: 641-642.

13. Barbara S, Sugarman B. Antipyresis and fever. Arch Intern Med 1990; 150: 1589-1597.

14. Hunter J. Study of antipyretic therapy in current use. Arch Dis Child 1973; 48: 313-315.

15. Tarlin L, Landrigan P. A comparison of the antipyretic effect of Acetaminophen and Aspirin. Amer J Dis Child 1972; 124: 880-882.

16. Colgan MT, Mintz AA. The comparative antipyretic effect of N acetyl-P-aminophenol and acetyl salicylic acid. J Pediatr 1957; 50: 552-555.

17. Eden AN, Kaufman A. Clinical compari son of three antipyretic agents. Amer J Dis Child 1967,114: 284-287.

18. Heremans G, Dehaen F, Rom M, Ramet J, Verboven M, Loeb H. A single blind parallel group study investigating antipyretic properties of ibuprofen syrup versus acetylsalicylic acid syrup in febrile children. Br J Clin Prac 1988; 42: 245-247.

19. Hurtwitz ES, Barett MJ, Bregman D, Gunn W. Public Health Service study of Reye syndrome and medications. Report of the main study. JAMA 1987; 257: 1905-1911.

20. Walson PD, Galleta G, Pharma D, Braden NJ, Alexander L. lburopfen, acetaminophen and placebo treatment of febrile children. Clin Pharmacol Ther 1989; 46: 9-17.

21. Wilson JT, Brown D, Kearns GL, Eichler VF, Johnson VA, Bertrand KM. Single dose placebo controlled comparative study of ibuprofen and acetaminophen antipyresis in children. J Pediatr 1991; 119:803-811.

22. Sheth UK, Gupta K, Paul T, Pispati PK. Measurement of antipyretic activity of ibuprofen and paracetamol in children. J Clin Pharmacol 1980; 20: 672-675.

23. Lesko SM, Mitchell AA. An assessment of the safety of Pediatric ibuprofen. JAMA 1995; 273: 929-933.

24. Walson PD, Galleta G, Pharm D, Braden NJ, Alexander L. Comparison of multidose ibuprofen and acetaminophen therapy in febrile children. Amer J Dis Child 1992; 146: 626-632.

25. Breart G. Jonville AP, Courcier S, Lassale C, Goehrs JM. A comparative efficacy and tolerance of ibuprofen syrup and acetaminophen syrup in children with pyrexia associated with infectious diseases and treated with antibiotics. Clin Pharmacol 1994; 46:197-201.

26. Ambedkar YK, Desai RZ. Antipyretic activity of ibuprofen and paracetamol in children with pyrexia. Br] Clin Prac 1985; 39:140-143.

27. Adam D, Stankov G. Treatment of fever in childhood. Eur J Pediatr 1994; 153: 394-402.

28. Esch AV, Henriette A, Moll VS, Steyerberg EW, Offringa M, Habbema DF. Antipyretic efficacy of ibuprofen and acetaminophen in children with febrile seizures. Arch Pediatr Adolesc Med 1995; 149: 632-637.

29. Kauffman RE, Sawyer LA, Scheinbaum ML. Antipyretic efficacy of ibuprofen *vs* acetaminophen. Amer J Dis Child 1992; 146: 622-625.

30. Sidler J, Frey B, Baerlocher K. A double blind comparison of ibuprofen and paracetamol in juvenile pyrexia. Br J Clin Pract 1990; 44 (Suppl 70): 22-25.

31. Ottolegni A. Pediatric use of dipyrone as an antipyretic agent. Minerva Pediatr 1971; 23:1981-1984.

32. The International Agranulocytosis and Aplastic Anemia Study. Risks of agranulocytosis and aplastic anemia. A first report of their relation to drug use with special references to analgesics. JAMA 1986; 256:1749-1757.

33. Discombe G. Agranulocytosis caused by amidopyrone: An unavoidable cause of death. BMJ1952,1:1270-1273.

34. Huguley CH. Agranulocytosis induced by dipyrone, a hazardous antipyretic and analgesic. JAMA 1964; 189: 938-941.

35. Rodriguez LES, Viveros HAA, Lujan ME. Assessment of the efficacy and safety of Nimesulide vs Naproxen in Pediatric patients with respiratory tract infection. Drugs 1993; 46 (Suppl): 226-230.

36. Cappella L, Guerra A, Landizi L, Cavazzuti GB. Efficacy and tolerability of Nimesulide and Lysine Acetyl Salicylate in the treatment of Pediatric acute upper respiratory tract inflammation. Drugs 1993; 46 (Suppl 1): 222-225.

37. Polidori G, Titti G, Pieragostini P, Comito A, Scaricabarozzi I. A comparison of Nimesulide and Paracetamol in the treat ment of fever due to inflammatory diseases of the upper respiratory tract in children. Drugs 1993; 46 (Suppl 1): 231-233.

38. Salzberg R, Giambonini S, Maurizio M, Roulet D, Zahn J, Monti T. A double blind comparison of Nimesulide and Mefenamic acid in the treatment of acute upper respiratory tract infections in children. Drugs 1993; 46 (Suppl 1): 208-211.

39. Mastersky J, Kass EH. Is suppression of fever or hypothermia useful in experimental and clinical infectious disease? J Infect Dis 1970; 121: 81-86.

40. Rremine SG, Me Ilrath DC. Bowel perforation in steroid treated patients. Ann Surg 1980; 192: 581-586.

41. Wilson JT, Ksantikul V, Harbison R. Death in an adolescent following an overdose of acetaminophen and phenobarbital. Am J Dis Child 1978; 132: 466-473.

42. Done AK, Yaffe SJ, Clayton JM. Aspirin dosage for infants and children. J Pediatr 1979; 95: 617-625.

43. Brown RD, Wilson JT, Kearns JL, Pharm D, Valarie F, Eichler RN. Single dose pharmacokinetics of ibuprofen and acetaminophen in febrile children. J Clin Pharmacol 1992; 32: 231-241.