

THE FEBRILE CHILD

This article was initially prompted by an exchange on the E-DRUG email list in January 1998 (see <http://www.essentialdrugs.org/>) about diclofenac and mefenamic acid use in children, for fever with or without pain. A clinician in Trinidad and Tobago noted that these agents were being recommended in his country and was worried about side effects. The response was surprisingly negative: one correspondent (writing from the United States) noted that mefenamic acid use was particularly prevalent in South Africa "despite the unfavourable risk/benefit ratio of mefenamic acid, the availability of safer drugs, and the doubts regarding the use of antipyretics in children with moderate fever". A German correspondent noted that it should not be used in children younger than 14 (which surprised the moderator, who recalled it being "a very popular analgesic for children", presumably when he practised in Zimbabwe). Another, from Pakistan, expressed the view that "it is not clear whether there is any benefit treating fevers lower than 41°C". A response from a United Kingdom drug information centre called both "unusual choices for children", claiming that mefenamic acid caused "convulsions in overdose, even with relatively small amounts". A Dutch physician was surprised "that so many people have simply forgotten why many countries refused or deleted "Ponstan" 20-30 years ago", citing the risk of haemolytic anaemia. An Italian also noted that neither anti-inflammatory was indicated for antipyretic use.

The question can therefore be posed: is South African practice in this regard unusual, or is there a basis in the literature for the prevalence of anti-inflammatory use in children, as an antipyretic?

The literature in this regard is confusing, and prolific. Even the most widely accepted advice – not to use aspirin in children (for fear of Reye's syndrome) is being challenged – a 1999 editorial in the *New England Journal of Medicine* called the decline in cases of Reye's seen after aspirin use was discouraged "a public health triumph".¹ However, a more recent paper concluded that "although aspirin may be associated with Reye's syndrome, it is unlikely, illogical and unfounded to state that aspirin causes Reye's syndrome".² With equally effective and safer options available, caution would still seem the best route. But, which agents are equally effective, and how safe are they?

The "evidence" for the efficacy of mefenamic acid is surprisingly thin, and old. Most reviews still quote a 1968 study by Weiss.³ Literature searches show other papers, in English and German from the same period and from the 1970s. More recent literature usually deals with ibuprofen, the first anti-inflammatory to be registered for this purpose in the United States (and available there without prescription). A French multicentre randomised double-blind study in 116 children found ibuprofen and paracetamol to be equally effective, as measured by a variety of endpoints: time elapsed between dosing and the lowest temperature (3.61 ± 1.34 hours for ibuprofen vs 3.65 ± 1.47 hours for paracetamol), extent of the temperature decrease ($1.65 \pm 0.80^\circ\text{C}$ vs $1.50 \pm 0.61^\circ\text{C}$), rate of temperature decrease ($0.52 \pm 0.32^\circ\text{C/hr}$ vs $0.51 \pm 0.38^\circ\text{C/hr}$) and the duration of temperature below 38.5°C (3.79 ± 1.33 hours vs 3.84 ± 1.22 hours).⁴ In both arms, an equally well-absorbed granule formulation was used. Rescue doses of paracetamol were permitted, and analysis was by intention-to-treat. Ibuprofen was also compared with aspirin or paracetamol in an open-label, multicentre trial, involving 351 children.⁵ Here the area under the curve (AUC) of percentage temperature reduction was the main criterion for efficacy, but a variety of quality of life measures were also included. Although ibuprofen appeared more effective by this criterion, it was also associated with significantly more adverse effects. Despite this, quality of life measures also favoured ibuprofen. However, when asked whether they would accept the same treatment again, the response from parents was in the affirmative in almost all cases – 90% for aspirin, 92% for ibuprofen and 95% for paracetamol.⁶ Perhaps most disconcertingly, a recent Cochrane Review has cast significant doubt on the efficacy of the apparent gold standard – paracetamol. Combining data from 12 trials ($n=1509$ participants) it concluded that "trial evidence that paracetamol has a superior antipyretic effect than placebo is inconclusive". It also noted that there was limited evidence that there was a difference in efficacy between paracetamol and physical methods (e.g. sponging, bathing or fanning). Crucially, it showed that there was insufficient evidence to show whether paracetamol influenced the risk of febrile convulsions.⁷ This confirmed the view expressed by the renowned paediatric intensivist, Frank Shann – summarised well for *Australian Prescriber*: "There is little evidence to support the use of

paracetamol to treat fever in patients without lung or cardiac disease, or to prevent febrile convulsions". A subsequent article on the same topic concluded, "there are good reasons, particularly related to toxicity, for limiting the use of paracetamol in children".⁸

Thus, if efficacy is doubtful (and substantially the same for all classes), what of toxicity? Short-term use of ibuprofen does not appear to be associated with significant renal problems, even in very young children (less than 2 years).⁹ This paper was but one from a series reporting on antipyretic use in more than 84 000 children. However, a large review of the literature still concluded that paracetamol should be the drug of first-choice, if and when it is decided to treat fever in a child.¹⁰ Both papers cautioned that there was no evidence to recommend simultaneous use of both agents. Two approaches have been used – either combining the drugs in a single dose or alternating paracetamol and ibuprofen (or, in this country, mefenamic acid). In a survey of 161 practitioners, it was found that 51% suggested the latter, alternating, regimen.¹¹ Although 29% claimed to do so in compliance with an American Academy of Pediatrics recommendation, no such policy exists. The authors also noted that the practice was more common in those with less than 5 years' experience, ascribing this to continued "anxiety about fever (fever phobia)". The pharmacodynamics of both paracetamol and ibuprofen are complex.^{10,12} Maximal fever reduction appears to occur 1-2 hours after the peak plasma concentration (C_{max}) is reached, usually 3-4 hours after dosing (this "temporal disequilibrium" suggesting the presence of an effect compartment). The magnitude of the effect is also related to the initial temperature (evidence of non-linear dynamics). Increased toxicity is also cited as a reason not to use alternating regimens.¹³

Perhaps the greatest danger though lies in the indiscriminate prescribing of paracetamol. In particular, imprecise instructions to give paracetamol "as needed" (or prn) must be avoided. Shann suggests a dose of 10-15mg/kg every 4 hours, to a maximum of 100mg/kg/day (with an absolute maximum of 4g/day for any patient, regardless of size).⁷ Precise identification of the product, the strength and dosage form, and the dose and interval is needed. A review of factors associated with toxicity in children also noted unintentional overdose with rectal preparations (due to variable absorption) and with multi-component paracetamol-containing preparations bought over-the-counter (and co-administered with prescribed paracetamol) and made many practical recommendations.¹⁴

A review of prescriptions for 47 103 members of a single South African medical aid in 1995 showed an alarming pattern of prescribing.¹⁵ Analgesics accounted for 12.3% of all items prescribed (and 14.2% of costs). Almost all such prescriptions (93.8%) were for non-opioid analgesics. Of these, 31.6% were for children aged less than 10 years. The 15 most frequently prescribed products accounted for 56.4% of all analgesic prescriptions, with the top 3 being the same brand-name multi-component product (containing paracetamol, codeine and promethazine in syrup form, and paracetamol, codeine, caffeine and meprobamate in the capsule and tablet forms; Stopayne[®]), together responsible for 23.4% of all analgesic prescriptions. Multi-component products made up 11 of the top 15. It is likely that much of this paediatric prescribing was for fever, with or without pain. It is also likely that a prescription audit today would show an equally alarming trend towards newer multi-component products, perhaps combining paracetamol and an anti-inflammatory. Hewson wrote that the "mild symptomatic benefit" of paracetamol "must be balanced against the increased incidence of mistaken dosage and toxicity".⁸ He also predicted that "if ibuprofen is used as widely as paracetamol then inevitably its toxicity and adverse effects will become a problem". The same can be said of any drugs in the class, including mefenamic acid.

Hewson also noted that "parents and doctors understandably need to feel they have something to offer sick, miserable children", but we would do well to consider his preferred multi-component prescription more often: "cuddles, comfort and fluids".

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Industry News

WORLD HEALTH PSYCHIATRY DAY

"I'm depressed", "I'm stressed", "She's suicidal", "He's suffering from post-traumatic stress disorder", and "I'm just not coping psychologically", are phrases common to daily conversation.

Is it a sign of the times, are these conditions more prevalent among South Africans, is the prevalence of mental disorders increasing and if so, what can be done? And how does one know if "dark days" are in fact depression – what makes for a healthy psyche?

Indeed, psychiatric and neurological disorders represent a significant area of medical need in South Africa and around the world. These disorders represent a great and increasing burden to sufferers, their families and healthcare systems.

In an effort to raise awareness of mental health, this year's World Health Psychiatry Day is on Thursday, October 10. So why not visit www.actioncns.com or <http://cns.ta.astrazeneca.net> information on a broad range of mental health issues, including: Depression, Schizophrenia, Epilepsy, Migraine, and Alzheimer's disease, to name but a few.

actionCNS.com is a unique, unbiased "one stop shop" global source of news and resources on Central Nervous System (CNS) disorders. Furthermore, you can register on this site to source specific CNS information, from news and education, to treatment guidelines, patient associations and CNS meetings around the world.

If you have problems accessing this site, or need further mental health related information, call AstraZeneca Business Unit Manager: Hugo van Zyl, on 011 797-6000. Alternatively contact the Depression and Anxiety Support Group on 011 783-1474 or the Schizophrenia Foundation on 0860 100-541.

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