CLINICAL PRACTICE

Risks and benefits of paracetamol antipyresis in young children with fever of presumed viral origin

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To examine whether antipyretic therapy in young children is associated with potential risks (interference with enhanced host defences at febrile temperatures) or benefits (improved comfort and behaviour), a randomised, double-blind, placebo-controlled trial of paracetamol was conducted among 225 children 6 months to 6 years of age who presented with acute ($\leq$4 days) fever ($\geq$38°C per rectum) without evident bacterial focus of infection. Parents were asked to give paracetamol liquid 10–15 mg/kg or placebo every 4 h as needed for fever and to avoid bathing, sponging, or other pharmacological agents. Parents kept temperature and symptom diaries and recorded changes in child comfort and behaviour according to a pretested, 5-category Likert-type questionnaire 1–2 h after every dose. There were no significant differences between treated and placebo groups in mean duration of subsequent fever (34·7 *vs* 36·1 h) or other symptoms (72·9 *vs* 71·7 h). Paracetamol-treated children were more likely to be rated by their parents as having at least a 1-category improvement in activity (38 *vs* 11%; p=0·005) and alertness (33 *vs* 12%; p=0·036) but no significant differences were noted in mood, comfort, appetite, or fluid intake. That overall improvement in behaviour and comfort with paracetamol was not impressive is underscored by the inaccuracy of parents' "guess" at the end of the trial as to which agent their child had received—45% correct guesses for paracetamol and 52% for placebo. The data suggest that the clinically relevant hazards and benefits of paracetamol antipyresis have been exaggerated.

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Introduction

The view that fever is beneficial persisted from the time of Hippocrates[1] until the 19th century, when Claude Bernard showed that animals died when their body temperature was raised to 5–6°C above normal.[2] Since then fever has generally been regarded as injurious to health, and antipyretic treatment is now routine, especially in children. However, there is no convincing evidence that naturally occurring fevers are harmful, even though many doctors and parents maintain that antipyretic treatment improves the febrile child's comfort and behaviour. In contrast, studies have clearly shown that fever helps laboratory animals to survive an infection whereas antipyresis increases mortality.[3-9] Moreover, there is considerable in-vitro evidence that a variety of human immunological defences function better at febrile temperatures than at normal ones.[10-14]

There have been few studies on whether interfering with these enhanced defences by means of antipyretic therapy has any clinically relevant adverse impact on the intact human host. Stanley et al reported that non-immune adult volunteers experimentally infected with rhinovirus and treated with therapeutic doses of aspirin were more likely to exhibit nasal viral shedding than those receiving placebo.[15] In a survey of 147 children in hospital because of bacterial infections, no difference in length of admission was found between patients receiving $\geq$2 doses of antipyretics during their stay and those receiving 0 or 1 dose.[16] A randomised trial of paracetamol *vs* placebo in children with chickenpox showed no significant differences in duration of symptoms (itching, activity, appetite) but a longer time to total crusting of lesions in paracetamol-treated than in placebo-treated subjects.[17]

On the basis of reported animal and in-vitro studies, we hypothesised that an adverse impact of antipyresis on immune function would most probably express itself clinically by an increase in severity or duration of symptoms. Symptom severity would be difficult to assess in a standard way across different types of viral illness (eg, coryza *vs* cough *vs* diarrhoea *vs* lethargy). In our assessment of the risks of paracetamol in young children with acute fever of presumed viral origin we therefore focused on the total duration of fever and of the other symptoms associated with each child's illness. The potential benefits we investigated included improvement in six specific aspects of the child's comfort and behaviour.

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Methods

The trial was randomised, double-blind, and placebo-controlled. Children 6 months to 6 years of age presenting either to a private paediatric group practice or to the emergency department of the Montreal Children's Hospital were considered eligible for the trial if they had fever of at least 38°C, were within 4 days of its onset, and had no evident bacterial focus of infection. Children subsequently diagnosed as having a bacterial infection during the same illness episode (eg, those whose urine or throat culture at the initial visit was positive) were considered ineligible and removed from the trial. Children with a history of febrile or afebrile convulsions and those with fever ≥ 41°C were excluded.

Children whose parents agreed to participate received the next consecutively numbered vial, which contained either paracetamol liquid (80 mg/ml) or a look-alike, taste-alike placebo. The consecutive study numbers (from 1 to 250) were linked to a series of 5-digit random numbers on a master list available only to the principal investigator (M. S. K.). Odd random numbers (*not* study numbers) were assigned to paracetamol, even numbers to placebo.

Parents were asked to give a volume of study medication equivalent to a paracetamol dosage of 10–15 mg/kg every 4 hours as needed for fever, exactly as they would normally use a known antipyretic, and to avoid other antipyretic measures, including bathing, sponging, and other drug therapy. Parents were specifically asked not to "double-dose" by giving any other than the trial agents; those who appeared hesitant or unwilling to refrain from using non-study antipyretics were discouraged from taking part in the study.

Parents used a simple diary to record rectal temperature and other symptoms four times a day until the child had been fever-free for at least 24 h. They were also asked to complete, 1–2 hours after each dose of study medication, a brief, pre-tested Likert-format questionnaire containing separate items concerning changes in the child's activity, alertness, mood, comfort, appetite, and fluid intake. These questionnaires were sent by post to the investigators after the child had recovered. To determine drug compliance and the duration of fever and associated symptoms (as recorded in the diaries) a research assistant interviewed the parents by telephone every 2 to 4 days after the index visit until the child's fever and other symptoms had resolved. Parents were also encouraged to volunteer whether they had given any aspirin or paracetamol or taken other antipyretic measures not prescribed by the study protocol. At the final interview the parents were also asked to guess whether the study drug received had been paracetamol or placebo.

On the basis of a clinically important mean difference of 1 day in duration of fever or other symptoms, a standard deviation of 2 days, a 2-tailed alpha (type I error rate) of 0·05, and a statistical power of 0·95, we estimated a sample size requirement of 210 subjects completing the trial. All children who received at least one dose of the study medication were included in an "intention-to-treat" analysis, irrespective of the total number of doses administered and of whether other antipyretic agents or measures were used.

The unusually long period of patient enrolment (Aug, 1982 to Aug, 1990) was necessitated by changes in study site, personnel, and funding base. During phase I (1982–83) patients were recruited only from the private office, with the trial being "piggy-backed" onto another study for which patients were being enrolled from the same office. Funding for the latter study ended in 1983, before we obtained the required numbers. Phase II began in 1987 with resumption of enrolment from both the private office and the emergency department on a part-time basis. After full and independent project support was obtained in November, 1989, full-time recruitment was possible at both study sites, including some evenings and weekends at the emergency department site (phase III). Enrolment was discontinued after the 1990 summer enterovirus season. Data on duration of fever and other symptoms were collected throughout the trial, but those concerning changes in child comfort and behaviour were restricted to phases II and III, and primarily to phase III.

The end-points of the study were mean duration of fever and other illness-associated symptoms (from the parents' diaries and telephone interviews) and the proportion of children who improved by at least one category in activity, alertness, mood, comfort, appetite, and fluid intake. Improvement scores were based on an average of the 5-category Likert-format questionnaires received for each child, with 1-category improvements being rated as "somewhat" better and 2-category improvements as "much" better.

Statistical testing was done with both the Student's t test and the Mann-Whitney U test for continuous variables and χ^2 tests for categorical variables. Since the t test and Mann-Whitney approaches gave virtually identical results, only the p values derived from the t tests will be presented in the results. Because the child comfort/behaviour improvement scores were obtained only during the latter stages of the trial (primarily phase III), sample sizes for these end-points were only approximately 40% of those for fever and symptom duration.

The study protocol received ethical approval from the Institutional Review Board of the Montreal Children's Hospital.

TABLE I—COMPARISON OF PARTICIPANTS AND NON-PARTICIPANTS*

—	Participants (n=225)	Non-participants (n=429)
Age (mo)	23·8 (SD 16·9)	28·1 (SD 19·0)
Sex (% female)	49·3%	49·9%
Temperature (°C)	38·9 (SD 0·9)	38·6 (SD 0·8)
Presenting symptoms:		
Respiratory	40·0%	34·2%
Gastrointestinal	16·9%	22·7%
Respiratory + gastrointestinal	12·4%	6·0%
Fever only	26·7%	33·5%
Other	4·0%	3·6%
Prior illness duration (h)†	28·9 (SD 23·2)	24·0 (SD 17·6)
Maternal education (yr)†	14·0 (SD 3·0)	14·2 (SD 2·9)
Green SES score†	65·3 (SD 9·6)	66·6 (SD 9·4)

*Non-participants include both refusals and withdrawals except where otherwise indicated.
†Results only for participants and withdrawals (ie, refusals are not included).

Results

654 children met the eligibility criteria, but over half (350) the parents refused to participate, mainly because of a reluctance to risk assignment to a placebo. Of the 304 children whose parents agreed, 79 subsequently withdrew from the study, the major reasons being disappearance of fever after enrolment (n = 28); parents' unease about being blind to therapeutic agent (n = 28); and objection by the other parent (usually the father) (n = 5). Of the 225 children who completed the study, 123 received paracetamol and 102

TABLE II—BASELINE COMPARISON OF PARACETAMOL AND PLACEBO GROUPS

Variable	Paracetamol (n=123)	Placebo (n=102)
Age (mo)	23·7 (SD 17·3)	23·9 (SD 16·5)
Sex (% female)	48·8%	50·0%
Temperature (°C)	38·9 (SD 0·9)	38·9 (SD 1·0)
Presenting symptoms		
Respiratory	39·8%	40·2%
Gastrointestinal	14·6%	19·6%
Respiratory + gastrointestinal	13·0%	11·8%
Fever only	26·8%	26·5%
Other	5·7%	2·0%
Prior illness duration (h)	30·3 (SD 25·0)	27·3 (SD 20·9)
Maternal education (yr)	14·1 (SD 2·8)	13·7 (SD 3·2)
Green SES score	65·8 (SD 9·7)	64·6 (SD 9·5)
No prior antipyretic treatment	23·8%	24·8%
Site (% emergency department)	48·0%	44·1%
Day/time		
Weekday day	64·2%	68·6%
Weekday evening	16·3%	16·7%
Weekend	19·5%	14·7%

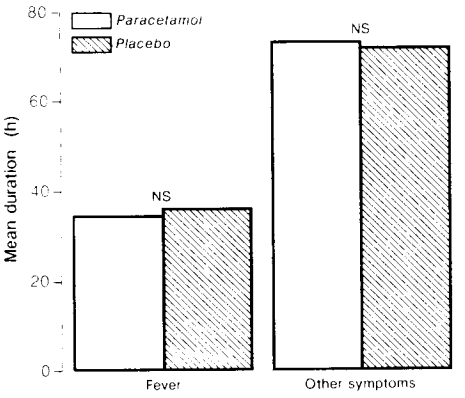

Fig 1—Duration of fever and other illness-associated symptoms in children receiving paracetamol *vs* placebo.

NS = non-significant.

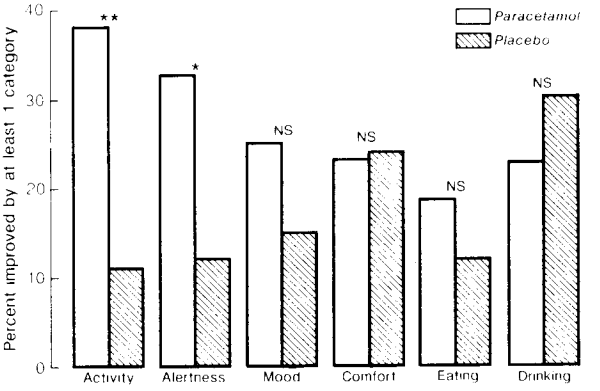

Fig 3—Percentage of children receiving paracetamol *vs* placebo who improved by at least one category in comfort/behaviour.

*p < 0·05; **p < 0·01.
NS = non-significant.

placebo. Of these 225, 81 were enrolled in phase I, 61 in phase II, and 83 in phase III; 104 from the emergency department and 121 from the private office; 149 on weekday days, 37 on weekday evenings, and 39 on weekends.

There were no important differences between participants and non-participants (refusals and withdrawals) in such variables as the child's age, sex, presenting temperature or symptoms, prior duration of illness, maternal education, or Green socioeconomic status (SES) score[18] (table I), despite our strong impression that immigrant families were more likely to refuse than were either English-speaking or French-speaking native Canadians.

The paracetamol and placebo groups were also extremely similar in these same baseline variables (table II). The two groups were also well balanced with respect to receipt of antipyretic agents before enrolment, study site, and day and time of enrolment. Few parents reported having given antipyretics or having taken other measures (bathing, sponging) not prescribed by the study protocol—2 in each group had given paracetamol, 1 in the placebo group had given aspirin; and 1 in each group used other measures.

The mean duration (in hours) of fever and of other symptoms was quite similar in the two groups, and the differences were statistically non-significant (fig 1). The 95% CI for the differences between the paracetamol and placebo groups were −10·0 to +7·1 h for duration of fever and −17·3 to +19.6 h for other symptoms. The results did not differ when analyses were stratified by age (< 24 months *vs* ≥ 24 months), temperature at presentation (< 39·0 *vs* ≥ 39·0°C), whether or not the child had received antipyretic treatment before enrolment, study site, day or time of enrolment, presenting symptoms, or phase of enrolment.

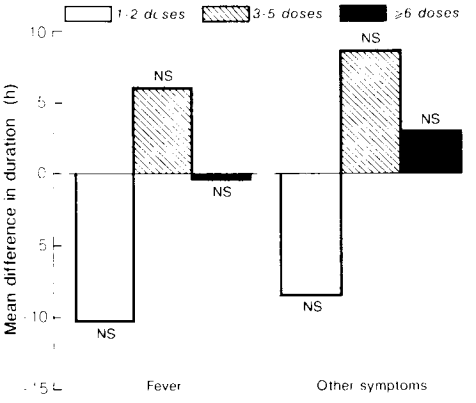

Fig 2—Differences (paracetamol minus placebo) in mean duration of fever and other symptoms according to number of doses received.

NS = non-significant.

Although the study protocol specified an "intention-to-treat" analysis that would include all those started on therapy, we also wished to ensure that we were not missing any harmful effects of paracetamol that might be evident only in those children receiving several doses. When children were categorised by number of doses received (1 or 2, n = 94; 3–5, n = 75; or ≥6, n = 56) no statistically significant differences in duration of fever or other symptoms were observed in any of the three groups, nor was there a clear trend across the three categories (fig 2).

Children who were treated with paracetamol were more likely to be rated by their parents as having at least a 1-category improvement in activity (38 *vs* 11%; p = 0·005) and alertness (33 *vs* 12%; p = 0·036) (fig 3). Paracetamol also seemed to have beneficial effects on mood and appetite but these effects were not statistically significant. About a quarter of the children in both treatment groups had 1-category improvements in comfort. Improvement in fluid intake was non-significantly greater in the placebo group. No child in either group experienced a febrile convulsion.

Parents had a low success rate in guessing which agent their child had received—correct guesses were obtained in only 45% of the paracetamol group and 52% of the placebo group. 27% of parents in the paracetamol group and 25% in the placebo group made incorrect guesses, and 28% and 24%, respectively, felt unable to attempt a guess. Children whose parents guessed correctly did not fare differently from those whose parents guessed incorrectly.

Discussion

Despite theoretical concerns that paracetamol might prevent the heightening of immune function that occurs at febrile temperatures, in standard therapeutic dosage the drug does not seem to prolong the duration of fever or other symptoms in young children with presumed viral infection. The drug also led to improvement in activity and alertness in about a third of treated children.

Because of the similarity of the treatment and placebo groups at baseline and the success of the blinding

procedures, we are reasonably confident of the internal validity of our findings. Our enrolment procedures and instructions concerning non-study drugs or antipyretic measures also satisfy us that potential differences were not substantially "diluted" by co-interventions not prescribed by the study protocol, even though parents' reports of such co-interventions are very probably underestimates.

Our high refusal rate merits some discussion about the external validity (generalisability) of our findings. Since the pattern of results (no illness prolongation, modest behavioural improvements with paracetamol) did not differ within subgroups defined by age, temperature at enrolment, or presenting symptoms, there is little reason for concern about generalising the results to non-participants in our study or even to other children. Further, the similarity in pattern of results across the three study phases spanning the 8-year recruitment period argues for the robustness of our findings over time.

We are somewhat less convinced, however, about whether the beneficial effects of paracetamol on comfort and behaviour can be generalised. We and others have reported on parental fever phobia,[19-21] but even so we underestimated the extent to which this fear would reduce enrolment; assurances by the research assistant of its safety and ethical approval by the hospital's Institutional Review Board did not allay the worry. It is possible, therefore, that parents who agreed to participate in the trial had already been rather unimpressed with the benefits of paracetamol, and thus participating children might have been a selective, paracetamol-unresponsive sample of the target population, in which case the benefits observed would have been an underestimation. With this caveat in mind, our results suggest that the clinically relevant risks and benefits of paracetamol antipyresis have both been exaggerated.

Our results may help paediatricians and other practitioners in several ways. First, parents can be reassured about the absence of apparent harm when paracetamol is given in therapeutic doses. At the same time parents should be educated that the drug does not necessarily make a child feel better and that treatment should perhaps be reserved for children who have the greatest need for relief, whether that relief is achieved by the antipyretic or analgesic effect of the medication. In other words, we should treat the child, not the thermometer. This is undoubtedly already the policy of many wise parents and physicians, and our results can be taken as support for that policy.

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From The Lancet

Frozen water-pipes

Those householders who aspire to the luxury of a hot and cold water system have during the recent severe frosts had to undergo in many instances a series of severe shocks to their nervous system through the repeated scares caused by frozen pipes. The principles of sanitary engineering, as applied to the domestic water system in our houses, are either so imperfectly understood or the elementary principles of hydrostatics, as applied to our domestic requirements, are so entirely ignored, that even in an ordinary frost considerable inconvenience and danger arise from the almost inevitable frozen pipes. During such prolonged and severe frost as we have recently had this trouble has necessarily been greatly aggravated. Many a household has been suddenly deprived of their water-supply, and have been obliged to borrow or beg even the water for drinking purposes from their more fortunate neighbours. . . . There is actually very grave danger in such defects in our domestic arrangements. The kitchen boiler may actually burst and explode with fatal violence, and such occurrences are matters of actual fact. Yet all this is avoidable by the simple observation of the most elementary principles of sanitary engineering as applied to water-supply. Every workman ought to be educated in these elementary principles, and every master of workmen engaged in business connected with sanitation or water-supply should be held responsible and rendered liable for any damage resulting from defects of workmanship or faulty construction.

(Jan 17, 1891)