

THE EFFECTS OF A COMPLEX HOMEOPATHIC MEDICINE COMPARED WITH ACETAMINOPHEN IN THE SYMPTOMATIC TREATMENT OF ACUTE FEBRILE INFECTIONS IN CHILDREN: AN OBSERVATIONAL STUDY

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Context: Children frequently suffer infections accompanied by fever, which is commonly treated with acetaminophen (paracetamol), a use not devoid of risk.

Objective: The effect of a complex homeopathic medicine (Viburcol, Heel Belgium, Gent, Belgium) was compared with that of acetaminophen in children with infectious fever.

Design: Non-randomized observational study.

Setting: Thirty-eight Belgian centers practicing homeopathy and conventional medicine.

Patients: Children <12 years old.

Interventions: Viburcol (drops) or acetaminophen (pills, capsules, or liquid form) for a maximum of 2 weeks.

Main Outcome Measures: Fever, cramps, distress, disturbed sleep, crying, and difficulties with eating or drinking. Symptoms were graded by the practitioner on a scale from 0 to 3. Severity of infection was evaluated on a scale from 0 to 4. Data were captured on body temperature, subjective impression of health status, time to first improvement of symptoms, and global evaluation of treatment effects. Tolerability and compliance were monitored.

Results: Both treatment groups improved during the treatment period. Body temperature was reduced by $1.7^{\circ}\text{C} \pm 0.7^{\circ}\text{C}$ with Viburcol and by $1.9^{\circ}\text{C} \pm 0.9^{\circ}\text{C}$ with acetaminophen; fever score (scale from 0 to 3) from 1.7 ± 0.6 to 0.1 ± 0.2 with Viburcol and from 1.9 ± 0.7 to 0.2 ± 0.5 with acetaminophen (all values mean \pm SD). The overall severity of infection (scale from 0 to 4) decreased from 2.0 ± 0.5 to 0.0 ± 0.2 with Viburcol and from 2.2 ± 0.7 to 0.2 ± 0.6 with acetaminophen. There were no statistically significant differences between treatment groups in time to symptomatic improvement. Viburcol was noninferior to acetaminophen on all variables evaluated. Both treatments were very well tolerated, but the Viburcol group had a significantly greater number of patients with the highest tolerability score.

Conclusions: In this patient population, Viburcol was an effective alternative to acetaminophen treatment and significantly better tolerated.

Key words: cramps, fever, noninferiority, nonrandomized, NSAID

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INTRODUCTION

Children frequently suffer infections accompanied by fever, which is treated by parents, visiting practitioners, or admittance to a hospital. Among the most common antipyretics are acetaminophen (paracetamol), which is currently recommended by the World Health Organization for children with a temperature $<39^{\circ}\text{C}$ ¹ and which is used as an over-the-counter drug in the treatment of a large number of infections of varying etiology and severity. However, the use of acetaminophen is not devoid of risk, particularly risk of hepatic damage from overdoses.^{2,3} The window between a pharmacologically active dose and a hepatotoxic dose for acetaminophen is small and may be reduced further when multiple doses are administered, in which case, the

harmful doses may be only just greater than the recommended maximum dose (90 mg/kg/day).⁴ Because the efficacy of drugs such as acetaminophen has not always been found to compensate for the risk of treatment,⁵ many parents and practitioners see complementary and alternative medicine as an appealing alternative to conventional therapies for the symptomatic treatment of minor illnesses. Such therapies are becoming increasingly popular in many parts of the world for several reasons. Surveys of treatment patterns show patients to turn to alternative treatments because of greater perceived safety and tolerability of medications, a closer patient-practitioner relationship, and greater patient influence over treatment decisions.⁶ However, complementary and alternative medicine is not a recent phenomenon, and, in certain European countries such as Germany, homeopathic remedies have been prescribed since the 1930s.⁶

Viburcol (Heel Belgium, Gent, Belgium) is a homeopathic preparation based on highly diluted plant extracts (listed in Table 1). Viburcol has long been used for the treatment of symptoms associated with mild viral infections such as the common cold. As with many homeopathic therapies, Viburcol has a long record of use and an attractive safety profile,⁷⁻⁹ but, as with most alternative medications, there is a need for

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Table 1. Constituents of Viburcol

Extracts, dilution	Content pro vial	Common use
<i>Camomilla</i> (Chamomile), D4	25.0 mg	Respiratory infections, gastric disorders
<i>Belladonna</i> (Deadly nightshade), D6	11.0 mg	Glandular, respiratory, gastric or urinary infections
<i>Dulcamara</i> (Woody nightshade); D6	25.0 mg	Fever, common cold
<i>Plantago major</i> (Rat-tail plantain), D4	25.0 mg	Headaches, gastric disorders
<i>Pulsatilla pratensis</i> (Pasque flower), D6	50.0 mg	Glandular, respiratory, gastric, or urinary infections; headaches; sleeplessness
Other substances		
Calcium carbonate, D8	75.0 mg	

adequate assessments of efficacy and tolerability in specifically designed studies.

The aim of the present investigation was to compare the effects of oral administration of the homeopathic preparation Viburcol (given as drops) with those of common acetaminophen therapy, administered as tablets, syrup or capsules, on the symptomatic treatment of febrile infections in children <12 years of age. The outcomes were analyzed to demonstrate the noninferiority of Viburcol on the effect on individual variables as well as on overall treatment effect.

Studies in complementary medicine are associated with specific difficulties that frequently make them less amenable than studies in conventional medicine to the randomized, double-blind study design. Homeopathic remedies are prescribed to a very wide range of patients, and a randomized trial design would run the risk of excluding patients not meeting certain predefined criteria. To reduce this risk and to reflect the broad spectrum of individuals treated in clinical practice, we chose a nonrandomized, observational study design. It is widely recognized that randomized and observational studies are complementary, not opposed, research methodologies.¹⁰

METHODS

This nonrandomized, prospective, observational cohort study included children 11 years of age or younger with acute infections accompanied by fever in 38 centers in Belgium. Each center was instructed to enroll 6 patients, 3 into the Viburcol group and 3 into the acetaminophen group. The choice of treatment in each individual patient case was left to the practitioner's discretion. Children were excluded if they were older than 11 years of age, if they were without symptoms at the time of initiation of treatment, and if they were enrolled at a center that failed to recruit patients to both treatment groups. Both therapies were administered orally. Viburcol was given as drops (from single-use plastic vials) at dosages decided in each individual case, depending on the age of the patient. Children under 1 year of age received 1 vial (3 × 5 drops) daily, children up to 5 years of age received 1 to 2 vials, and older children 2 vials daily. Acetaminophen was administered as pills, capsules, or liquid form. Treatment was to continue for a maximum of 2 weeks.

All patients and their caretakers were informed about the background and purpose of the study, which was conducted in full compliance with the principles of the Declaration of Helsinki and with the regulations for the conductance of observational studies (Bundesanzeiger Federal Gazette No 299, December 1998).

Patients were examined at first visit, and demographic data were collected together with data on temperature, symptoms, severity, duration of illness at the time of presentation, possible previous treatments, and overall status at the time of presentation. The final visit was to take place within 2 weeks of treatment initiation. At this visit, treatment effects were evaluated, and changes to treatment regimen were documented together with the reasons for possible changes, state of the patient, compliance, tolerability, and occurrence of any adverse events. Discontinuation of therapy before the final visit was possible on grounds of adverse events, unsatisfactory treatment effects, or the disappearance of further symptoms.

Treatment efficacy was evaluated by the practitioner on the following variables: fever, cramps, distress, disturbed sleep, crying, and difficulties with eating or drinking. The expression of symptoms was graded on severity on a scale from 0 to 3, of which 0 indicated no symptoms, 1 indicated mild symptoms, 2 indicated moderate symptoms, and 3 indicated severe symptoms. Severity of infection was evaluated on a 5-point scale from 0 to 4. In addition, body temperature was recorded at baseline and at the final visit.

Furthermore, subjective impression of health status was assessed by the child caretakers as 1, well; 2, moderately well; 3, unwell; and 4, very unwell. Time to first improvement of symptoms was recorded, and a global evaluation of treatment effect was performed by the practitioner in a dialogue with the respective child caretaker. Five degrees of effect were distinguished: "excellent," "good," "moderate," "none," and a worsening of symptoms, at which, "excellent" indicated a complete regression of symptoms.

Tolerability was graded on a 4-point scale, from "excellent" (indicating a complete regression of symptoms), "good," and "moderate" to "poor." Compliance (rated as child caretaker's compliance) was evaluated on a similar 4-point scale. Patients were monitored for adverse events, which were documented descriptively.

Table 2. Baseline Characteristics

Variable	Viburcol (n = 107)	Acetaminophen (n = 91)	P value for between-group comparison before/ after PS adjustment
Male sex n (%)	53 (49.5%)	50 (54.9%)	ns
Age, years (mean ± SD)	3.3 ± 2.6	3.6 ± 2.5	ns
Age classes n (%)			
Infants, <1 year	22 (20.6)	14 (15.4)	
Toddlers, 1-5 years	70 (65.4)	62 (68.1)	
School children, 6-11 years	15 (14.0)	15 (16.5)	
Adjunctive treatments (%)	57 (53)	62 (68)	0.04/0.13
Degree of fever, n (%)			0.030/0.27
Low	14 (13.1)	11 (12.1)	
Moderate	77 (72.0)	51 (56.0)	
High	16 (15.0)	27 (29.7)	
Very high	0 (0.0)	2 (2.2)	
Duration of symptoms at time of presentation, n (%)			ns
<1 day	17 (15.9)	14 (15.4)	
2 days	48 (44.9)	43 (47.3)	
3 days	25 (23.4)	19 (20.9)	
4-7 days	15 (14.0)	11 (12.1)	
1-2 weeks	2 (1.9)	4 (4.4)	
Subjective impression of health status, n (%)			0.007/0.29
Well	10 (9.4)	3 (3.3)	
Moderately well	47 (43.9)	35 (38.5)	
Ill	47 (43.9)	41 (45.0)	
Very ill	3 (2.8)	12 (13.2)	

Statistical Evaluation

The risk of bias inherent in observational studies¹¹ was reduced by applying a propensity score (PS) adjustment.¹² This is a method to construct matched strata that balance observed covariates, allowing for the application of standard statistical methods.

A PS was estimated for each patient using logistic regression, and patients were divided into 4 strata according to PS scores. The following variables were used as underlying covariates: age, sex, size, weight, temperature, duration of illness, severity of individual symptoms, overall severity of illness, subjective impression of health status, pretreatment, accompanying illnesses, and use of adjunctive therapy. Treatment groups were compared after adjustment for PS using a 2-way ANOVA model for covariates based on interval data and Cochran-Mantel-Haenszel test for covariates with dichotomous values. For all the above variables, differences between treatment groups were not significant, with a significance criterion of $P > .05$ after the PS adjustment Table 2.

The noninferiority analysis included the quantified scores for fever, cramps, distress, disturbed sleep, crying, difficulties with eating/drinking, and total score of these variables, as well as the quantified assessment of the overall severity of infection and the temperature. Noninferiority of Viburcol was defined as a situation in which the left limit of the 1-sided 95% confidence interval for differences between the treat-

ment groups should not cross the border of 10% of changes in the respective treatment, with an error probability of 0.05. This corresponded to a value of -0.3 for the separate variables analyzed, -0.4 for the severity of infection score, and -1.8 for the total score in the study.

This was not a confirmatory study, and, thus, every individual efficacy and safety criterion was assessed. A multivariate analysis was not carried out because this method is not applicable to the demonstration of noninferiority using 1-sided confidence intervals. Data were analyzed with SAS version 8.1 (SAS Institute, Inc., Cary, NC, 2000).

RESULTS**Patients**

A total of 198 patients at 38 centers were included in the study, 107 in the Viburcol group and 91 in the control group. Each center treated between 3 and 12 patients. Baseline criteria for the 2 patient groups are given in Table 2. The groups were balanced for age, sex, height, and weight as well as for duration of illness and frequencies of most recorded indications. The most common indications were rhinitis (25%), bronchitis (22%), otitis media (18%), and/or tonsillitis (14%), with multiple indications possible but infrequent (15% of cases). The only significant difference in indications between the groups was a greater frequency of rhinitis in the Viburcol

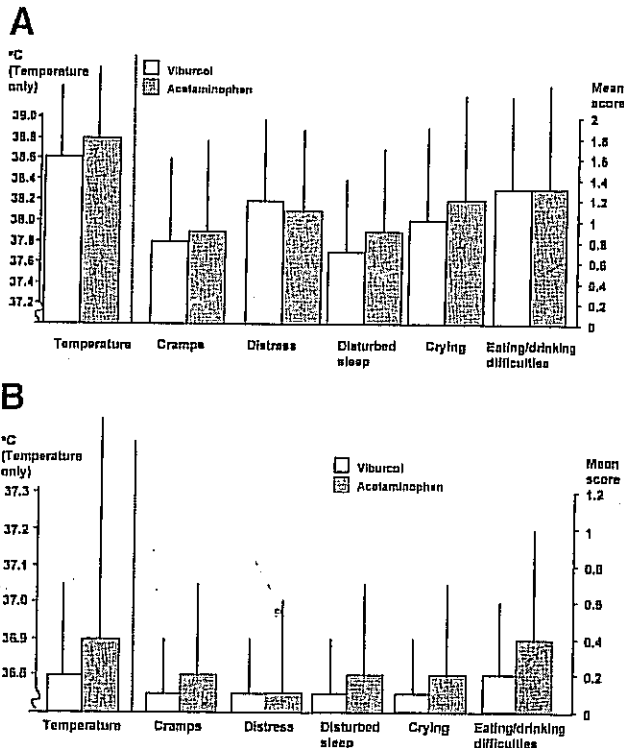


Figure 1. Mean score (mean temperature for the variable temperature) of 6 efficacy variables (A) before and (B) after treatment with either Viburcol (open bars) or acetaminophen (shaded bars). Lines indicate SD.

group compared with the acetaminophen group (30.8% vs. 17.6%, respectively; $P = .03$ for the comparison).

Differences between patient groups at baseline were observed before adjusting for PS on the variables temperature, degree of fever, subjective impression of health status, and use of additional medication Table 2. However, these differences were no longer statistically significant (significance criterion, $P < .05$) after the PS adjustment Table 2. This was also true, although on the border of significance, for the differences in frequency of rhinitis in the 2 groups ($P = .051$ after adjustment). Drugs additional to study medications for treatment of the underlying infections were allowed and were given to 52.3% of Viburcol patients and 65.9% of acetaminophen patients. The spectrum of medications was very wide and consisted of mostly herbal remedies such as Euphorbium (Heel Belgium), menthol, cough syrups, and others in both groups, with small differences between groups. Euphorbium was used in 5 patients (2.5%), and the homeopathic preparation Oteel (a herbal remedy used mainly for otitis media; Heel Belgium) was used in 6 patients (2 in the Viburcol group and 4 in the acetaminophen group). Four patients (4%) in the Viburcol group received different varieties of penicillin compared with 11 patients (12%) in the acetaminophen group.

Patients received study treatment for a mean of 8 days (2-15 days) in the Viburcol group and for 7.6 days (2-15 days) in the

acetaminophen group. Twenty-six patients (24.3%) and 17 patients (18.7%) in the Viburcol and the acetaminophen group, respectively, discontinued treatment before the end of the study for reasons of symptom disappearance. Daily doses of acetaminophen varied greatly among individual patients: among the infant group, from 100 mg to 720 mg; among toddlers, from 180 mg to 1,050 mg; and, among school children (5-11 years of age), from 200 mg to 1,600 mg. The maximal Viburcol dose differed less among age groups than the maximal acetaminophen dose: With the exception of infants, all age groups received up to 3 to 4 vials daily. Most infants (95%) received <1 vial; most older children received 2 to 4 vials daily. In 17 patients, the acetaminophen dose was reduced during the study period; in the Viburcol group, 3 patients had their doses increased, and, for 8 patients, doses were reduced during the treatment period.

Treatment Efficacy

Both treatment groups improved markedly during the treatment period, measured on all variables (Figure 1). At baseline, the variables with the highest scores (most severe symptoms) were distress, crying, and eating/drinking difficulties (Figure 1A). The degrees of symptomatic improvements, measured as change from baseline, were similar in both groups and for all individual variables (Figure 2). A reduction in body temperature was seen in both groups ($-1.7^{\circ}\text{C} \pm 0.7^{\circ}\text{C}$ with Viburcol and $-1.9^{\circ}\text{C} \pm 0.9^{\circ}\text{C}$ with acetaminophen), which was accompanied by a reduction in fever score from 1.7 ± 0.6 to 0.1 ± 0.2 in the Viburcol group and from 1.9 ± 0.7 to 0.2 ± 0.5 in the control group (all values mean \pm SD).

Similarly, the overall severity of infection decreased in both treatment groups during the course of the study: from 2.0 ± 0.5 to 0.0 ± 0.2 in the Viburcol group and from 2.2 ± 0.7 to 0.2 ± 0.6 in the control group (all values mean \pm SD).

There were no statistically significant differences between the treatment groups ($P = .55$ for the comparison) in time to

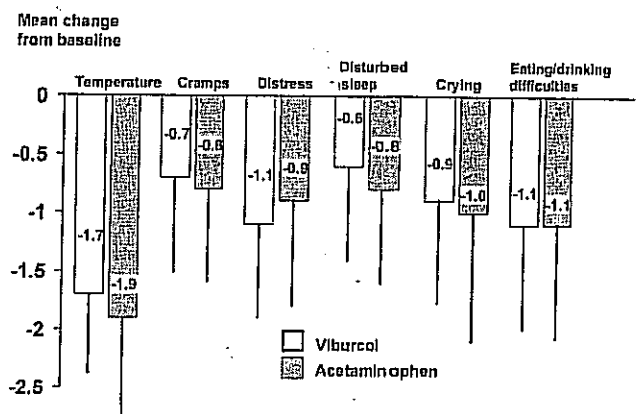


Figure 2. Mean change from baseline in score (temperature for the variable temperature) from baseline to study end for 6 variables after treatment with either Viburcol (open bars) or acetaminophen (shaded bars). Lines indicate SD.

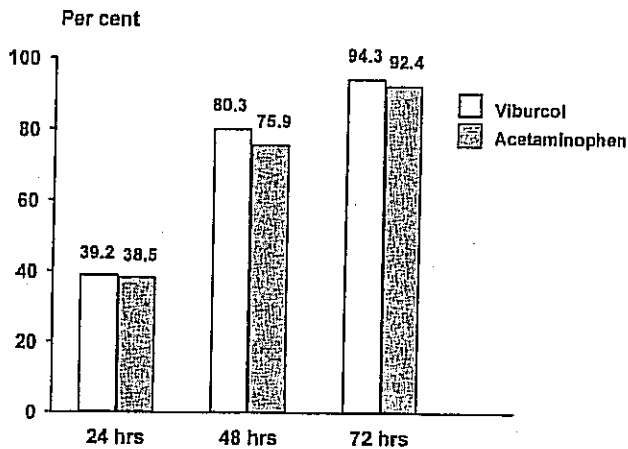


Figure 3. Time to symptomatic improvement. Percentage of patients with symptomatic improvement after 24 hours, 48 hours, and 72 hours of treatment with Viburcol (open bars) and acetaminophen (shaded bars), respectively.

symptomatic improvement (Figure 3). In both groups, approximately 40% of patients improved within 24 hours of the first treatment dose and 80% within 2 days of treatment.

The global evaluation of treatment effect revealed statistically significant differences in favor of Viburcol. Treatment was evaluated as "excellent" in 69.2% of cases for Viburcol, compared with 57.1% for acetaminophen ($P = .008$ for the comparison). Only for 2.8% of Viburcol patients and 12.1% of acetaminophen patients did the global evaluation of treatment result in scores of "moderate" or lower.

For the noninferiority analysis, differences between treatments (acetaminophen group and Viburcol group) were analyzed on data adjusted for PS. The results are shown in Figure 4. The confidence intervals for all scores were well within the predefined boundary, including the confidence interval for the total score, of which the noninferiority boundary was set at -1.8 . As seen in Figure 4, most differences were in favor of Viburcol, with the exception of disturbed sleep, regarding which, the differences between treatment groups were slightly in favor of acetaminophen therapy. The analysis was not designed to detect superiority of one treatment over the other, but it is notable in Figure 4 that the left boundary of the 1-sided 95% confidence interval fails to cross the boundary of unity and remains within the interval in favor of Viburcol for several variables: difficulties with eating or drinking, total score, and overall severity of infection.

Tolerability

Both treatments were very well tolerated, but the number of patients who rated tolerability as "excellent" was significantly higher ($P = .004$) in the Viburcol group (93.3%) than in the acetaminophen group (80.8%). All patients in both groups rated treatment tolerability as "excellent" or "good." No adverse events were reported in any patient group. A further sign of the good tolerability of both treatments was the compli-

ance rates (rated as child caretakers' compliance). Two thirds (67.3%) of patients in the Viburcol group were rated as "excellently" compliant, compared with 60.4% in the acetaminophen group. Compliance was rated as "good" in 29.0% of cases for the Viburcol group and 35.2% for the acetaminophen group. These differences between treatment groups were not significant.

DISCUSSION

The main conclusion from this nonrandomized, observational study is that the homeopathic preparation Viburcol, consisting of highly diluted plant extracts, is noninferior to acetaminophen treatment for the symptomatic treatment of acute infections accompanied by fever in children aged <12 years. Both treatment groups improved significantly during the study period, and the percentage of patients who reported improved symptoms after 3 days exceeded 90% in both groups. In the noninferiority analysis, Viburcol fulfilled the criteria for noninferiority on all variables studied. In fact, the analysis indicated superiority of Viburcol on the variables difficulties with eating or drinking, total score, and overall severity of infection. However, because the study was not designed to detect superiority, the data cannot be taken as proof of significantly greater benefits from the homeopathic therapy compared with acetaminophen regimens. Although this very interesting question of the possible superiority of Viburcol over conventional treatments must await a specifically designed study, the consistency of the current results on all variables strongly supports the noninferiority conclusion.

Mean doses of acetaminophen and Viburcol were within the range usually recommended for children at the respective ages. A large percentage of patients in both groups received

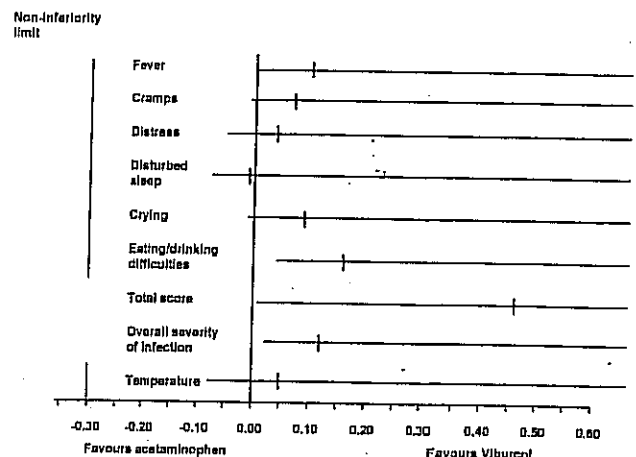


Figure 4. Noninferiority analysis of Viburcol and acetaminophen on clinical variables, total score, and overall severity of infection. Vertical lines indicate difference between treatment groups. Negative values favor acetaminophen. The left boundary of the 1-sided confidence interval is shown. The noninferiority limits for severity of infection (-0.4) and for total score (-1.8) fall outside the scale of this graph.

additional medications. This was expected because the study design allowed for therapies aimed at treating the underlying illnesses. It is an open question to which degree these therapies may have influenced the outcomes of the study, but it is unlikely that the noninferior effects of Viburcol can be attributed to differences in additional medications between the groups. Additional treatments were given to fewer patients (52.3%) in the Viburcol group than in the acetaminophen group (65.9%). Furthermore, a very wide spectrum of (mainly herbal) additional remedies was used, and the number of patients receiving each specific agent was low.

This was an observational cohort study, and patients were not randomized. The design was chosen to capture the widest range of patients possible, in a setting as close as could be attained to everyday clinical practice. Homeopathic therapies are administered to a very broad range of patients, who are often active in their choice to opt for homeopathic therapies instead of conventional medicine. Furthermore, homeopathic treatments are highly individualized. These considerations and the chosen study design indicate that the patients in our study population who received the homeopathic medication might show differences from those receiving conventional treatments. This possibility was statistically compensated for by the use of PS analysis, by which patients were stratified according to the probability of receiving one or the other treatment. As it turned out, baseline variables were highly similar between the treatment groups, with only minor differences observed before PS adjustment. After PS correction, no statistically significant differences between treatment groups at baseline remained.

The option of a homeopathic therapy for the symptomatic treatment of acute febrile infections in children expands the alternatives for practitioners and child caretakers concerned about the trade-off between risks and benefits with acetaminophen therapy in children. Acetaminophen is more popular than aspirin for pain relief and for symptomatic relief in cases of mild infections such as the common cold.¹³ However, acetaminophen is often over used in the treatment of childhood fever,¹⁴ and the hepatotoxicity associated with high doses is a source of concern. There are also indications that the risk of acetaminophen-induced hepatotoxicity is increased in acutely malnourished children,¹⁵ which is relevant in light of the common use of acetaminophen in developing countries. Product information recommends a maximum daily dose of 60 mg/kg, but it is not uncommon for children to receive 90 mg/kg/day during hospital stays.^{1,16} There is argument for restricting the size of packs as well as for limiting over-the-counter availability of acetaminophen-containing drugs.¹⁷ However, despite this high use, there are few reports on risks and benefits of acetaminophen specifically in children with febrile infections. The findings in the present work seem reassuring because no adverse events were reported in any group, and both groups had high tolerability ratings.

Homeopathic medications have a very good tolerability record,^{6,7,9} which was further corroborated by the Viburcol findings. The fact that more practitioners and child caretakers rated tolerability as "excellent" for the homeopathic treatment than for the acetaminophen treatment is a sign that

there may be perceived differences in tolerability even when no adverse events are present. The results are further reassuring in light of the recent discussion about potential harmful effects of certain herbal remedies,¹⁸ which are clearly not relevant to Viburcol, which is a formulation based on the principles of homeopathy rather than those of herbal medicine.

It is interesting to note that the time to first improvement was not significantly different in the 2 groups. Three fourths of patients reported symptomatic improvement within 48 hours in both groups. Given the pharmacologic actions of acetaminophen, the low rates (<40%) of patients reporting symptomatic improvements within 24 hours may be an unexpected finding; however, the lack of differences between the groups indicates that the efficacy of both treatments were highly similar from the first dose given.

The study variables were evaluated by the practitioner, and it should be acknowledged that there may be a risk of bias and subjective interpretations of variables less easily quantified than, for example, fever. We believe that the large number (38) of centers should smooth the overall data. Also, practitioners, who see many patients and have a long experience with the investigated symptoms, are less liable to bias than an emotionally involved child caretaker. With a mean age of the children around 3.5 years, the patients' own statements as to health status are unlikely to be as reliable as judgments by an experienced practitioner.

In summary, for patients opting for a homeopathic remedy rather than conventional therapy, our results indicate that the homeopathic preparation Viburcol is an effective and well-tolerated alternative to acetaminophen for the symptomatic treatment of children with acute infections accompanied by fever.

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