Trying to improve compliance with prophylactic penicillin therapy in children with sickle cell disease

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Aims To evaluate compliance with prophylactic penicillin therapy in sickle cell disease (SCD) in children.

Methods Forty-five children aged 37 ± 19 (9–84) months [mean ± s.d; range] with homozygous SCD were recruited. After a baseline period of 2 months the patients were randomized to either the intervention or non-intervention group. The intervention consisted of a slide show explaining the pathogenesis of sickle cell disease and its complications; weekly phone calls by the clinic social worker; and a calendar. Compliance was again evaluated after the 2 month intervention period and after a further 2 month monitoring period without intervention. Compliance was monitored using the Medication Event Monitoring System. At the end of the 6 months, parents in both groups completed a questionnaire the aims of which were to determine knowledge and understanding of sickle cell disease and previous experience with infection. Patient admissions to the hospital during the study were recorded.

Results Compliance during the 2 month baseline assessment was 66.0 ± 32.5 (1.3–98.2)% and 69.3 ± 25.4 (19.8–96.5)% in the intervention ($n = 13$) and non-intervention ($n = 10$) groups respectively ($P = 0.79$). During the next 2 months, compliance in the intervention group ($n = 11$) was 79.0 ± 31.4 (11.0–100.0)% and in the non-intervention group ($n = 9$) was 66.0 ± 20.2 (42.2–96.8)% ($P = 0.297$). In the final 2 month monitoring period compliance was 82.0 ± 34.7 (3.8–100.0)% and 65.8 ± 25.3 (25.0–98.2)% in the intervention ($n = 7$) and the non-intervention ($n = 6$) groups respectively ($P = 0.366$). No statistically significant differences were found when comparing compliance between the groups.

Conclusions Compliance with prophylactic antibiotic therapy in children with sickle cell disease is highly variable and its evaluation is problematic.

Keywords: prophylactic penicillin, sickle cell disease

Introduction

Before the introduction of prophylactic penicillin therapy, meningitis, pneumonia and septicaemia caused by *Streptococcus pneumoniae* and other encapsulated bacteria were the major causes of death among children with sickle cell disease (SCD), with those under 3 years of age being at highest risk [1, 2]. In a randomized, double-blind multicentre trial, children with SCD were given prophylaxis with oral penicillin. In that study Gaston *et al.* [3] showed a significant decrease in the incidence of pneumococcal septicaemia. Based upon this study, screening for SCD in the neonatal period [4] is performed in many centres in North America and prophylactic therapy with oral penicillin is started by the age of 4 months. However, less than 50% of these children continued to take oral antibiotics regularly after a 3 month period [5].

The evaluation of patient compliance includes biological markers, tracer compounds, pill count, patient reports, physician reports and the computerized compliance monitor [6, 7]. Various methods have been used to improve patient compliance with prescribed therapy. The results of these attempts have been varied [6, 7]. We report here a randomized trial in children with SCD for whom oral prophylactic penicillin twice daily was prescribed. The goal of the study was to establish a simple method of improving compliance in this patient population.

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Methods

Forty-five children with SCD aged 37 ± 19 (range 9–84) months at the time of enrollment, receiving prophylactic penicillin twice daily, regularly attending the sickle cell clinic at the Hospital for Sick Children, participated in the study. Compliance was monitored using the Medication Event Monitoring System (MEMS, APREX Corporation, CA), a pill bottle that monitors the timing and frequency of bottle openings. After a baseline period of 2 months the patients were randomized to either the intervention or the non-

intervention group. Patients in the intervention group attended a slide show at the time of randomization, consisting of 15 slides describing the pathophysiology of SCD and the infections associated with the disease, the various complications and the importance of prophylactic antibiotic therapy. Each parent whose child was randomized to the intervention group received stickers designed by a cartoonist and a calendar to be used as a diary to document compliance with the therapy. Furthermore, these stickers were used to encourage children older than 3 years of age to participate in their own therapy. A social worker from the clinic called these families weekly for the duration of the 8 week intervention period. During this conversation, the social worker asked specific questions about the prophylactic antibiotic treatment, the general health of the child, other medications given to the patient and family problems were asked. After the 2 month intervention period, patients were invited to the clinic, compliance was evaluated and then monitored for a further 2 months without intervention. Patients in the non-intervention group were invited to the clinic every 2 months, at which time the medication was dispensed and compliance evaluated, without any additional intervention.

At the end of the 6 months study period parents in both groups completed a questionnaire whose aims were to determine knowledge and understanding of SCD, previous experience with infection, and socioeconomic and educational levels of the caregivers. Patient admissions to the hospital during the study were recorded. Statistical analysis was performed using a Student's *t*-test for the comparison between the two groups of patients and are expressed as mean $\pm$ s.d. For the analysis of Data from the questionnaire were analyzed using Student's *t*-test and ANOVA were used.

Results

Eighteen patients were initially given oral penicillin in a liquid form; in five cases (28%) the MEMS device was unreadable because liquid penetrated into the device. We then changed the penicillin formulation from liquid to tablets. Of the 45 children who received penicillin tablets, 13 (28%) had problems with ingestion of tablets and were removed from the study. In seven more cases (15%) patients were taken off the study because of parental refusal of follow up. One patient's MEMS device broke (non-intervention group), so no data were available. Another patient randomized to the intervention group did not receive social work calls due to miscommunication and, therefore, was excluded from the study.

Compliance during the 2 months' baseline assessment was 66.0 ± 32.5 (1.3–98.2)% [mean $\pm$ s.d.; range] and 69.3 ± 25.4 (19.8–96.5)% in the intervention ($n=13$) and non-intervention ($n=10$) groups, respectively ($P=0.791$). During the next 2 months, compliance in the intervention group ($n=11$) increased to 79.0 ± 31.4 (11.0–100.0)% and in the non-intervention group ($n=9$) was 66.0 ± 20.2 (42.2–96.8)% ($P=0.297$). In two patients in the intervention group and one patient in the non-intervention group data were not available after the baseline period due to broken MEMS devices.

In the final 2 month monitoring period during which active intervention was not given, compliance was 82.0 ± 34.7 (3.8–100.0)% and 65.8 ± 25.3 (25.0–98.2)% in the intervention ($n=7$) and non-intervention ($n=6$) groups, respectively ($P=0.366$). Once again, data for this period were not available in four patients from the intervention and three patients from the non-intervention groups because of broken MEMS devices.

No significant differences were found when comparing compliance within the non-intervention group during the three periods. In the intervention group when comparing baseline with the intervention period, compliance increased, but again not significantly ($P=0.068$); no other differences were found.

Six children required hospital admission during the study, three from each group. From the intervention group one patient was admitted with a urinary tract infection due to *Klebsiella oxytoca* that was not sensitive to penicillin, one with influenza and one with a sickle cell vaso-occlusive crisis. From the non-intervention group three patients were admitted with sickle cell vaso-occlusive crises.

Comparing the baseline compliance of the patients with the answers given by the parents on the questionnaire that they filled out upon concluding their participation in the study, no significant differences were found with regard to any of the questions including knowledge and understanding of sickle cell disease, marital status, socio-economic and educational levels of the caregivers.

Discussion

Non-compliance is a recurring, common problem among pediatric patients [8]. Several methods have been used to improve compliance with chronic medications:; education, family and social supports, reminders and rewards [9].

In our study we found that the baseline compliance was 67.4 ± 29.1%—higher than in other similar studies. This seemingly higher compliance in this population could be as a result of the emphasis that is put on prophylactic antibiotic treatment in our clinic. Our sickle-cell patients are visiting the clinic every 2 months for half an hour visit, where a physical examination is performed, and the importance of the prophylactic antibiotic therapy is discussed.

Baseline compliance was extremely variable, ranging from 1.3–98.2%—an unexpected finding that cannot be predicted from a clinical evaluation. This emphasizes the importance of compliance monitoring in the clinical setting. During the 2 months of intervention, compliance in the intervention group increased to 79.0 ± 31.4 (11.0–100.0)%, possibly as a result of the intervention. This increment was not significant ($P=0.068$), probably because of the small sample size ($n=11$). In the intervention group, among the patients with a baseline compliance less than 80%, the mean baseline compliance was 38.6 ± 27.8 (1.3–77.7)% and increased during the intervention period to 65.2 ± 38.2 (11.0–100.0)% ($P=0.075$). This may imply that patients with high baseline compliance do not need further intervention while patients with lower compliance will benefit from intervention.

Of the six hospital admissions during the study, there were no infections due to encapsulated bacteria, however, it is a small group of patients, and a prolonged observation period is probably needed before one is able to assess the effectiveness of the therapy.

This is the first published study evaluating the compliance of sickle cell children with prophylactic antibiotic therapy using the MEMS device. However MEMS devices are not recommended to be used with liquids, a fact that was not known to us and nor to the engineers in APREX corporation before the study. That compelled us to change from liquid suspension, which most patients were using previously, to tablet form. After this change 28% of the children in our study dropped out because of difficulties in ingesting the tablets. It is important to note that this specific study was performed among a pediatric population, and the children not infrequently dropped the MEMS device. These factors were not known to us before the initiation of the study, and we think they reflect the difficulties many researchers have when trying to assess compliance, particularly among pediatric patients.

In conclusion, compliance with prophylactic antibiotic therapy in children with sickle cell disease is variable and its evaluation is problematic. This is a pilot study with a small number of patients, and therefore a larger study that addresses some of the problems that we encountered is warranted.

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(*Received 19 May 1997, accepted 14 January 1998*)