Piracetam for the treatment of sickle cell disease in children - a double blind test

The Piracetam Study Group*

ABSTRACT
Sickle cell disease (SCD) occurs frequently in the Saudi population and is often associated with high morbidity and disabling complications. The search for drugs to ameliorate the clinical presentation of SCD has been going on for the last 3 decades. Aim: The objective of this investigation was to study the effect of piracetam on the clinical presentation, hematological and relevant biochemical parameters in children of two different age groups suffering from severe SCD.

Study design: A double-blind, placebo controlled, randomised multicentre trial conducted in different regions of Saudi Arabia.

Patients and methods: Children (3-12 years) suffering from severe SCD as judged from severity index of 6 or more were enrolled in the study. One hundred and one children were included of whom 87 (79 SCA and 8Sβ-thal) completed the one year treatment protocol. The drug/placebo was received from UCB Company in coded boxes and administered as intravenous infusion during crises (300 mg/kg/day) and orally (160 mg/kg/day) during follow-up period. The baseline clinical data was recorded and hematological and biochemical parameters were assessed. The patients were treated and followed-up for a one year period and the follow-up was conducted every 8-12 weeks. On completion of the study period, the codes were decoded and the patients were grouped according to whether they had received piracetam or placebo and on the basis of age i.e. 3-6 years and 7-12 years of age.

Results: The results were separately analyzed for the 3-6 and 7-12 years age groups. In terms of age, weight, height, SI, number of blood transfusions received and number of hospitalization both groups (i.e. placebo and piracetam) were statistically homogeneous. The results of the placebo and Piracetam treated groups were analyzed and a statistically significant decrease was observed in SI, number of crises, blood transfusion requirements and extent of hospitalization in the groups treated with piracetam compared to the placebo group. No differences were seen in the levels of hematological and biochemical parameters and Hb F level.

Conclusion: Piracetam can be used for the amelioration of the clinical presentation of SCD. Even after discontinuation of the drug it's beneficial effects remain for several months.

Keywords: Sickle cell disease, Hb S/β-thal., piracetam, Nootrophil.

Sickle cell gene occur at a high frequency in the Eastern and Western Provinces of Saudi Arabia and the sickle cell disease in some children, particularly those from the Western Province is associated with high morbidity and severe complications. These children are frequently affected by incapacitating episodes of vaso-occlusive, infarctive and hemolytic crises which entails their absence from school, admission in hospital and frequent blood transfusion requirement. Frequently the episode of vaso-occlusive crises may lead to other complications including multiple organopathy, impaired growth and development. The management of children suffering from sickle cell disease (SCD) has been the concern of all clinicians caring for these patients. Several agents have been tried for the treatment, though with limited benefit or toxic side effects. Agents such as hydroxyurea and erythropoietin that have been used successfully in adults suffering from SCD have not yet been approved for use in children due to the associated cytotoxicity or myeloproliferative effects.

Piracetam (2-oxo-1-pyrrolidine acetamide), a cyclic derivative of ω-amino butyric acid has long been used for the management of psychosensative syndromes with no known toxic side effects. It is...

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We conducted a double blind, multicentre clinical trial in different regions of Saudi Arabia, with the major aim to study the effect of piracetam on the clinical presentation (i.e. disease severity, number of crises, extent of hospitalization, blood transfusion requirements) and hematological and relevant biochemical parameters, in children suffering from severe sickle cell disease. This paper reports our findings and discusses the benefit of piracetam in the treatment of SCD.

The study design. The study was a double blind, placebo controlled, multicentre study conducted to test the efficacy and usefulness of piracetam in children with SCD need to be confirmed in large double blind clinical trials.

Patients and methods. The study was conducted in 13 centres in 10 different regions of Saudi Arabia. Initially a total of 101 SCD patients, all suffering from a severe form of sickle cell disease (SCD and Hb S/β-thalassemia) as judged from a severity index (Table 1) of 6 or more, were enrolled in the study. The ages of the children ranged from 3-12 years and were grouped into 3-6 year and 7-12 year groups. This study was initiated on 20th August 1992 and the children were enrolled as they came to the hospital/out-patient clinics for follow-up. The study was double blind and randomized, where patients received piracetam or placebo and neither the patient nor the clinicians knew what the patient was receiving. Care provided for all patients was exactly the same. The study lasted until 2nd January 1994 and each patient was treated for a period of up to 1 year. Only 87 of the children completed the full study. Others (16) in different areas dropped out at an early stage of the study. The patients failed to come for follow-up and no reason was given. It was not expected that the patients faced any side effects, since this would have brought them to their clinician even if they did not continue the therapy.

Of the 87 children who completed the study, 79 had SCA and 8 had Hb S/β-thal. as judged from the results of hematological parameters and Hb A2 level (see below). The majority (79) were from the Western Province while 8 were from the Eastern Province. The purpose of the study was explained to the parent or guardian of the patient and informed consent was obtained for enrolment. Only those who volunteered were included in the study. The clinical data and complications in the patients were used to calculate the Severity Index10 (Table 1) prior to inclusion in the study. Severity Index (SI) was designed as a quantitative measure of the severity of SCD using the parameters listed in Table 1. The presence of a certain complication was given a score and for some parameters such as painful crises, number of blood transfusion requirements and number of hospitalizations, a point score was added for each time the complication occurred. The scores over a period of one year were added and the sum was the SI.

The treatment protocol. The drug (piracetam or placebo) was provided by UCB Company in numbered (coded) boxes, each box containing enough drug/placebo for one patient’s treatment for one year. The company’s representative in Riyadh

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3-6 Years Group</th>
<th>7-12 Years Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (F:M)</td>
<td>(13:10) (6.13)</td>
<td>(10.15) (8.12)</td>
</tr>
<tr>
<td>No. of SS</td>
<td>21 16</td>
<td>23 16</td>
</tr>
<tr>
<td>No. of Sβ</td>
<td>2 4</td>
<td>2 4</td>
</tr>
<tr>
<td>Age (Yrs)</td>
<td>4.5±1.2 4.5±1.1</td>
<td>9.4±1.7 9.2±1.7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>106.8±17.5 106.2±10.2</td>
<td>118.9±13.4 109.9±47.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>16.3±6.6 14.3±5.4</td>
<td>20±3±4 19±3.9</td>
</tr>
<tr>
<td>No. of crisis</td>
<td>4.6±3.7 3.0±1.2</td>
<td>5.0±3.6 4.2±1.5</td>
</tr>
<tr>
<td>No. of blood Tx</td>
<td>2.5±2.9 1.9±2.0</td>
<td>3.1±4.4 1.1±1.7</td>
</tr>
<tr>
<td>No. of hospitalization</td>
<td>3.5±3.0 3.4±3.0</td>
<td>4.3±3.4 2.9±2.1</td>
</tr>
<tr>
<td>Gini score</td>
<td>8.3±2.2 8.8±2.3</td>
<td>9.6±2.2 9.3±3.6</td>
</tr>
<tr>
<td>SI</td>
<td>16.3±9.9 12.9±5.5</td>
<td>18.6±9.5* 13.2±5.0</td>
</tr>
</tbody>
</table>

(*p = 0.05 statistically significant)  ( ) = numbers

Table 1 - Parameters of severity index (SI) of SCD.

<table>
<thead>
<tr>
<th>Reversible complications</th>
<th>Score</th>
<th>Chronic complications</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin level 6-10 g/l</td>
<td>1</td>
<td>Stroke/deep venous thrombosis</td>
<td>1</td>
</tr>
<tr>
<td>&lt;6.0 g/l</td>
<td>2</td>
<td>Interstitial lung disease (decrease PO2)</td>
<td>1</td>
</tr>
<tr>
<td>Reticulocyte cytopenia</td>
<td>1</td>
<td>Cardiomyopathy</td>
<td>1</td>
</tr>
<tr>
<td>Bilirubin &gt; 2 Norm</td>
<td>1</td>
<td>Gallstones</td>
<td>1</td>
</tr>
<tr>
<td>LDH &gt; 2 Norm</td>
<td>1</td>
<td>Papillary necrosis</td>
<td>1</td>
</tr>
<tr>
<td>No. of severe painful crisis per year</td>
<td>1</td>
<td>Aseptic necrosis</td>
<td>1</td>
</tr>
<tr>
<td>No. of transfusion per year</td>
<td>1</td>
<td>Impotence</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short stature</td>
<td>1</td>
</tr>
</tbody>
</table>

Modified from Ref. No. 10
Table 3 - Efficacy comparison in children 3-6 years and 7-12 years

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3-6 Years Group</th>
<th>7-12 Years Group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Piracetam Mean (SD)</td>
<td>Placebo Mean (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Piracetam Mean (SD)</td>
<td>Placebo Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>S1</td>
<td>16.4±9.9</td>
<td>12.9±5.5</td>
<td></td>
</tr>
<tr>
<td>- Baseline</td>
<td>18.6±9.5*</td>
<td>13.2±5.1*</td>
<td></td>
</tr>
<tr>
<td>- After Rx.</td>
<td>0.001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>- p</td>
<td>NS</td>
<td>0.0001</td>
<td>NS</td>
</tr>
<tr>
<td>No. of Crisis</td>
<td>4.6±3.7</td>
<td>3.0±1.1</td>
<td></td>
</tr>
<tr>
<td>- Baseline</td>
<td>5.1±3.6</td>
<td>4.2±1.5</td>
<td></td>
</tr>
<tr>
<td>- After Rx.</td>
<td>2.2±1.9*</td>
<td>4.3±2.9*</td>
<td></td>
</tr>
<tr>
<td>- p</td>
<td>0.001</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>No. of hospitalization</td>
<td>3.5±3.0</td>
<td>3.4±3.0</td>
<td>4.3±3.4</td>
</tr>
<tr>
<td>- Baseline</td>
<td>1.9±2.6</td>
<td>2.2±1.9</td>
<td></td>
</tr>
<tr>
<td>- After Rx.</td>
<td>2.4±2.5</td>
<td>1.5±2.0</td>
<td></td>
</tr>
<tr>
<td>- p</td>
<td>0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>No. of Blood transfusion</td>
<td>2.3±2.9</td>
<td>1.9±2.0</td>
<td>3.1±4.4</td>
</tr>
<tr>
<td>- Baseline</td>
<td>0.9±1.9</td>
<td>1.0±1.5</td>
<td></td>
</tr>
<tr>
<td>- After Rx.</td>
<td>1.2±2.3</td>
<td>0.7±2.0</td>
<td></td>
</tr>
<tr>
<td>- p</td>
<td>0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Disp. Rx: Treatment
*Difference between the results in piracetam and placebo group is statistically significant (p<0.05).

The study. Patients were admitted to hospital and clinical assessment was carried out and recorded. To standardize the procedure for estimation of different parameters all determination, except estimation of hematological parameters, were carried out in Riyadh, on samples sent by air freight. Blood samples (5-10ml) were drawn and used freshly for the estimation of hematological parameters and red cell indices using Coulter Counter. Reticulocyte counts were obtained for each sample. The red cells, buffy coat and plasma were separated by centrifugation and the washed red cells were used to prepare fresh hemolysate using cold distilled water. The red cells were stored at 4°C and the buffy coat and plasma were frozen at -20°C. All samples were sent to Riyadh and all the following analysis were carried out in Riyadh. The hemolysate was subjected to electrophoresis at alkaline and acid pH, to confirm the hemoglobin status and to determine Hb A₂ and Hb F level. The plasma was used for the estimation of relevant biochemical parameters which included liver function test profiles and total LDH using autoanalyser, American Monitor “Parallel”. The LDH isoenzymes were also estimated by electrophoresis using kits from Helena. During the hospitalization period daily clinical evaluation was carried out until the day of discharge. The same protocol was followed for any subsequent vaso occlusive crises. On discharge, the patients were maintained on an oral, prophylactic treatment dose of 160 mg/kg/day and were followed regularly every 8-12 weeks for the total period of the study. At each visit clinical history was recorded, the patients were clinically assessed and routine hematological and biochemical parameters were assessed at each visit. At the end of the study period the UCB Company provided the drug code i.e. whether placebo or piracetam, and the children were grouped according to whether they were on placebo or piracetam. Of the total children, 48 had received piracetam and 39 had received placebo as was unveiled upon deciphering the codes. The data was separated for the two groups and further grouping was carried out on the basis of age (i.e. 3-6 years and 7-12 years). The data was entered on the main frame computer at the Computer Centre, King Saud University, Riyadh and the analysis was conducted using the Statistical Analysis System (SAS). Mean and standard deviations were calculated for each group. The statistical significance of the difference in the results of any two groups were obtained by applying the students t-test, Wilcoxon Scores, Van Der Waerdon 1-way (chi square approximation), and Kolmogorov-Smirnov test. p less than 0.05 was considered statistically significant. At the end of the study, the patients in Riyadh were followed regularly every 3 months for the whole year.

Results. The results of hemoglobin electrophoresis, red cell indices, Hb A, and Hb F levels were used to classify the patients as either sickle cell anemia (Hb SS) or Hb S β-thal. patients. The former group has Hb SF electrophoresis pattern, mean cell volume (MCV) and mean cell hemoglobin (MCH) in normal levels and normal Hb A level. While the Hb S β-thal. patients also with Hb SF electrophoretic pattern, have reduced MCV and MCH and elevated Hb A₂. The children treated with piracetam/placebo in this study, were grouped on the basis of age into 3-6 year and 7-12 year age groups in an attempt to determine if there were any differences in the effect of the drug/placebo on the hematological parameters and clinical presentation in the two age groups. The baseline data was compared in the piracetam and placebo groups and the results are presented in Table 2. As can be
Table 4 - The effect of piracetam and placebo treatment on hematological and biochemical parameters in sickle cell disease patients.

<table>
<thead>
<tr>
<th>Age Group (Yrs)</th>
<th>3-6 years</th>
<th>7-12 years</th>
<th>3-6 years</th>
<th>7-12 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Tx</td>
<td>After Tx</td>
<td>Before Tx</td>
<td>After Tx</td>
</tr>
<tr>
<td>RBC (x 10^12/l)</td>
<td>2.6±0.5</td>
<td>2.7±0.5</td>
<td>2.6±0.46</td>
<td>2.7±0.4</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>7.7±1.5</td>
<td>8.4±2.0</td>
<td>7.9±1.1</td>
<td>7.8±1.0</td>
</tr>
<tr>
<td>WBC (x10^9/l)</td>
<td>13.9±6.3</td>
<td>11.7±14.8</td>
<td>14.0±5.2</td>
<td>12.2±6.2</td>
</tr>
<tr>
<td>Retic (%)</td>
<td>6.0±5.9</td>
<td>6.9±6.1</td>
<td>8.4±5.0</td>
<td>8.6±5.1</td>
</tr>
<tr>
<td>Hb F (%)</td>
<td>13.5±4.3</td>
<td>11.4±8.0</td>
<td>10.0±6.9</td>
<td>8.3±6.0</td>
</tr>
<tr>
<td>Bilirubin (mmol/l)</td>
<td>23.9±19.0*</td>
<td>30.0±22.0</td>
<td>33.2±23.2</td>
<td>47.6±20.0</td>
</tr>
<tr>
<td>LDH (U/l)</td>
<td>369.5±190.0*</td>
<td>378.1±185.0</td>
<td>416.2±100.0</td>
<td>423.1±105.0*</td>
</tr>
<tr>
<td>LDH1 (%)</td>
<td>29.4±9.5</td>
<td>29.5±8.1</td>
<td>37.7±9.5</td>
<td>31.0±9.2</td>
</tr>
<tr>
<td>LDH2 (%)</td>
<td>28.1±7.6</td>
<td>24.8±6.8</td>
<td>31.6±7.6</td>
<td>32.9±7.5</td>
</tr>
<tr>
<td>Haptoglobin (g/dl)</td>
<td>0.24±0.4</td>
<td>0.23±0.7</td>
<td>0.17±0.2</td>
<td>0.10±0.2</td>
</tr>
<tr>
<td>PCV (%)</td>
<td>0.23±0.65</td>
<td>0.23±0.4</td>
<td>0.23±0.03</td>
<td>0.24±0.03</td>
</tr>
</tbody>
</table>

*P < 0.05  
**1-t-test was carried out to compare the value of each parameter before treatment with the value after treatment. No statistically significant difference was found (p>0.05). 
(2) t-test was carried out to compare the value of each parameter in the piracetam group with the placebo group. No statistically significant difference was found except for total bilirubin (*p<0.05).

seen, no statistically significant differences are encountered in the basal data and both the groups on placebo and piracetam were statistically homogeneous, except the SI which was higher in the piracetam group (7-12 years old) (p< 0.05).

The efficacy was checked by comparing the severity index, the number of crises, the number of hospitalizations and the number of blood transfusions requirements prior to and during treatment with piracetam or placebo in the 3-6 and 7-12 year age groups separately. The results are presented in Table 3. In each age group there was a statistically significant decrease in the piracetam group compared to the placebo group.

The effect of piracetam and placebo on the hematological and biochemical parameters in the 3-6 years and 7-12 year age groups were assessed and the results prior to and during treatment are presented in Table 4. Hb F level fluctuated throughout the treatment period, but did not alter significantly. No statistically significant differences were encountered in the piracetam group compared to the placebo group.

The study was completed after one year of treatment and was discontinued in all areas, except Riyadh, where a follow-up was possible due to the easy access to the blood samples for laboratory analysis. Children in Riyadh (on piracetam) followed for up to one year after completion of the study, still showed a significant improvement in their clinical presentation and disease severity as the severity index remained low. Mothers of the children on piracetam requested more drugs at each visit as they were very satisfied with the improvement in their child's health status during treatment. One child (6 year old girl) with a deep ulcer on her cheek which did not improve despite regular treatment, improved dramatically when treated with piracetam.

Discussion. This study was conducted on a group of SCD children suffering from a severe disease as judged from the SI values. Over several years of studies on SCD patients, we designed the SI to provide a quantitative measure of the severity of the disease [EL-Hazmi et al - personal observation]. When assessed over a period of a whole year the SI could easily distinguish between patients suffering from a severe disease from those suffering from a mild one. On the other hand, during various treatment modalities we found that SI was a useful measure to assess the beneficial effect or otherwise of the drug being used.10-12

This multicentre double blind trial, showed the beneficial effect of piracetam on the clinical presentation of SCD, where SI, blood transfusion requirements, extent of hospitalization and number of crises decreased significantly and no such effect was seen in the group on placebo. This effect was obvious in both the 3-6 and 7-12 year old group. Of special notice is the fact that some SCD patients who were suffering from 10 or more crises/year prior to piracetam treatment, had none or very few crises during the treatment and the severity index decreased significantly. In the majority of children on piracetam no episodes of crises occurred during the treatment period and the patients felt generally healthy and active. A similar effect was not seen in the placebo group. This confirms that piracetam has a significant ameliorating effect on SCD patients.

Piracetam has long been used for the treatment of

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3-6 years</th>
<th>7-12 years</th>
<th>3-6 years</th>
<th>7-12 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb F (%)</td>
<td>10.0±6.0</td>
<td>12.0±6.0</td>
<td>13.0±6.0</td>
<td>11.0±6.0</td>
</tr>
<tr>
<td>LDH (%)</td>
<td>30.0±5.0</td>
<td>26.0±4.0</td>
<td>25.0±3.0</td>
<td>23.0±2.0</td>
</tr>
<tr>
<td>PCV (%)</td>
<td>0.23±0.4</td>
<td>0.24±0.5</td>
<td>0.23±0.6</td>
<td>0.24±0.7</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.5±4.3</td>
<td>11.4±8.0</td>
<td>10.0±6.9</td>
<td>8.3±6.0</td>
</tr>
<tr>
<td>WBC (x10^9/l)</td>
<td>30.0±22.0</td>
<td>33.2±23.2</td>
<td>47.6±20.0</td>
<td>423.1±105.0*</td>
</tr>
<tr>
<td>Retic (%)</td>
<td>6.0±5.9</td>
<td>6.9±6.1</td>
<td>8.4±5.0</td>
<td>8.6±5.1</td>
</tr>
</tbody>
</table>

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Piracetam has long been used for the treatment of
psycosesenescent syndromes, where it exerts a special effect on nerve cells. In SCD, piracetam inhibits or even reverses the sickling phenomenon. This is not achieved by increasing Hb F as is the case with hydroxyurea and erythropoietin, since during piracetam treatment no significant Hb F elevation was observed. This is believed to be through its action on the actin-spectrin network in the red cell membrane. It has been shown that piracetam, in addition to reversing and inhibiting sickling, also suppresses platelet activity. The exact mechanism of piracetam action, however, still remains to be unveiled.

Over two decades piracetam has been used for the treatment of SCD. In 1976, De Melo and co-workers reported the effect of piracetam treatment on 20 SCD patients with age range 15-18 years as “satisfactory clinical evolution in 80% of patients”; this included reduction in hepatomegaly, splenomegaly, abdominal and generalized pain. In 1977, De Araujo and Nero studied 12 patients (6 children 1-6 years of age and the rest 7-35 years of age) and reported that piracetam oxygenated red cells, reversed sickling and alleviated crises in a few hours. A few years later the same authors reported satisfactory results in thirty patients and compared the results with a similar number of untreated patients. There was a marked reduction in painful crises, blood transfusion requirements and hospitalization. Our results are in agreement with these and other studies that reported a beneficial effect of piracetam on the clinical presentation of SCD. In contrast several reports exist in literature where no beneficial effect of piracetam treatment were reported. These contradictory reports may result from (i) doses of piracetam used for treatment and (ii) whether clinical or hematological assessment of the effect of the drug was carried out. On the other hand, no effect of piracetam on the biochemical and hematological parameters was observed. The liver function tests, the hematological parameters, the total LDH level and the isoenzyme of LDH did not show any significant change, though there were several fluctuations. The hemolytic pattern did not change specifically, as judged from the levels of total and direct bilirubin and LDH. However, the clinical improvement in the patients is significant. This is probably related to the well established antisickling properties of piracetam, which can also reverse sickling as shown both in in vivo and in vitro studies.

The interesting observation that when treatment with piracetam was discontinued, the children felt better for several months (as judged from low SI, general health of the patient’s and the patient’s history) suggests that a continuous treatment with piracetam may not be necessary. One year of treatment followed by a 6 month gap and repeat treatment may be equally beneficial.

Of special interest is the fact that the parents insisted on continuation of the therapy. This shows the satisfaction they felt and no one can feel this more than the parents themselves, who are highly sensitive to the child’s condition. In addition, no toxic side effect was observed, as judged from the hematological parameter values, platelets and reticulocyte count and general clinical presentation of the patient. We, therefore, strongly recommend the use of piracetam for the amelioration of the clinical presentation of SCD in children. Similar trials on adults need to be initiated to judge the efficacy of piracetam in this group.

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References


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