The King Faisal Specialist Hospital Medical Journal 3(4), 1983, 233-236

A PRELIMINARY REPORT ON PIRACETAM IN SICKLE CELL ANEMIA: A DOUBLE-BLIND CROSSOVER CLINICAL TRIAL AND EFFECTS ON ERYTHROCYTE SURVIVAL

MUHAMMAD A. MIKATI, MD,* HASSAN M. SOLH, MD,* DENISE E. DERYAN, MD,* ITAF F. SAIHLI, MD† AND IBRAHIM A. DABBOUS, MD‡

ABSTRACT

Nine subjects with sickle cell disease were treated with Piracetam in the dosage of 80 mg/kg p.o. divided into four doses per day for a period of 5 months and with placebo for a similar period on a double-blind crossover basis. The number of pain crises during the treatment period was significantly less than the number of attacks during the placebo period. Red blood cell survival measured in seven patients failed to show any significant change during the administration of Piracetam. These results suggest that Piracetam may be a useful drug in the amelioration of pain crises in sickle cell anemia.

KEYWORDS Pyrrolidinones Anemia, Sickle Cell Erythrocytes

Introduction

Piracetam (2-oxo-1-pyrrolidine acetamide), a drug shown to protect against hypoxic brain damage and used as a psychotropic agent,[1] has been shown to have beneficial effects in sickle cell anemia (SCA).[2-6] Its exact role, however, still remains controversial.[7,8] We are reporting the results of a double-blind crossover study on the effects of Piracetam in a group of children with SCA. To our knowledge, this has not been done previously. The effects of Piracetam on red blood cell (RBC) survival are also reported.

Materials and Methods

Subjects

Thirteen children with SCA (ages 4–15 years) were entered into the clinical study between January 1981 and February 1982. Four were dropped because of a short or irregular follow-up. The remaining nine were five females and four males. Seven patients, four males and three females, were entered into the experimental study of RBC survival (ages 2–15 years, mean 9 years). All our patients were Moslem Arabs from or living in Lebanon. The form of SCA seen in Lebanon is generally more severe than found in most of Saudi Arabia.

*Resident
Department of Laboratory Medicine
American University Medical Center
Beirut, Lebanon
†Senior Research Assistant
Department of Laboratory Medicine
American University Medical Center
Beirut, Lebanon
‡Associate Clinical Professor, Department of Pediatrics
American University Medical Center, Beirut, Lebanon
Locum Pediatrician, Hematology Oncology
King Faisal Specialist Hospital and Research Centre

Methods

The diagnosis of SCA was established by hemoglobin electrophoresis in the patients and their parents (Goldberg modification of the starch gel electrophoresis).[9]

In the clinical trial the subjects received either Piracetam capsules 80 mg/kg/day p.o. in four daily doses or capsules containing 300 mg of lactose, also in four daily doses. After taking one type of capsule (chosen randomly) for 5 months, the patients took the second type for a similar period. The capsules were indistinguishable and the investigators, patients, and their families had no knowledge of their contents except after the termination of the study and analysis of the data. In the experimental study the seven patients, initially observed for 6 months, subsequently received Piracetam capsules 80 mg/kg/day p.o. for another 6 months. All

patients were seen at least once monthly. A careful history and physical examination were performed, and complete blood and reticulocyte counts were recorded. RBC survival was determined before and 3 months after starting therapy using chromium-51 after the method of Mollison and Veal[10] as modified by Read and Gilbertsen.[11] Informed consent was obtained from the parents of all subjects.

Results

In the clinical trial the average duration of observation was 5 months for the treatment period and 4 for the placebo. The average number of pain crises per subject per month was 0.89 on Piracetam and 1.85 on placebo (Table 1). This difference was statistically significant (Student t test, $p < 0.05$).

TABLE 1. *Number of pain crises*

Patient	Number of pain attacks per patient per month on Piracetam	Number of pain attacks per patient per month on placebo
1	0.17	0.00
2	0.12	0.25
3	0.00	0.60
4	0.00	0.40
5	0.00	0.60
6	0.00	0.00
7	0.00	0.00
8	0.00	0.00
9	0.00	0.00

$t = 1.78$
SD = 0.20
Critical t value, one variable, at $P = 0.05$ is 1.64.

The severity of the pain crisis was much less on the drug than on the placebo, but since this parameter is highly subjective and cannot be quantitated, it was not taken into consideration in the final analysis of the data.

Discussion

Statistical analysis of our data shows definite amelioration of painful crisis with Piracetam. However, because of the variable natural course of SCA, the relatively short study period, and the small number of patients, our results should be interpreted with caution and reservation. Piracetam in the dosage of 80 mg/kg/day had no significant effect on RBC survival, hemoglobin concentration, or reticulocyte count (Table 2). Similar observations were also reported by de Melo,[2] de Araujo and Nero,[3] and Skondia and Bick[5] with respect to hemoglobin concentration and reticulocyte count.

TABLE 2. *The effect of Piracetam on hemoglobin concentration, reticulocyte count and RBC survival*

Patient	Hemoglobin (gm dl) Off	Hemoglobin (gm dl) On	Reticulocyte count (%) Off	Reticulocyte count (%) On	$T\frac{1}{2}$ ^{51}Cr RBC survival* Off	$T\frac{1}{2}$ ^{51}Cr RBC survival* On
1	7.4	7.4	7	7	4.6	6.2
2	10	10	4.7	0.7	12.6	17.6
3	9.5	9.4	2	2.2	9.5	7.3
4	8.0	8.2	6	7	6	10
5	8.2	8.4	—	—	10.7	8.6
6	9	9	—	—	6.6	7
7	6.7	9.7	15	5	7.6	9.5

* $T\frac{1}{2}$ ^{51}Cr RBC survival: RBC half-life. A group of 15 normal individuals was studied in our laboratories as controls. $T\frac{1}{2}$ ^{51}Cr RBC varied between 25 and 36 days with an average value of 28.9 days and a standard deviation of 2.6

In 1976, de Melo[2] reported reduction of hepatomegaly and abdominal and generalized pain in 80 percent of 22 patients with SCA on Piracetam. Similar clinical improvement was observed in the 12 patients of de Araujo and Nero in 1977.[3] In 1978 de Araujo *et al.*[4] reported marked reduction in pain crises, blood transfusion requirements, and hospitalizations in 30 SCA patients treated with Piracetam as opposed to a similar number of untreated subjects. RBC survival, studied in two patients, was prolonged in one and unchanged in another. In 1981, Skondia and Bick[5] using 160–200 mg/kg/day of Piracetam in four divided doses found the drug highly effective in reducing the number, severity, and duration of pain crises in all seven patients studied. Using the same large dosage in 12 subjects, Bick and associates reported that Piracetam significantly reduced the number, severity, and duration of vaso-occlusive crises.[6] However, all these clinical studies were not double-blind and generally not well controlled.

The mode of action of Piracetam in SCA was initially reported to be through inhibition and reversal of the sickling process.[3] This was not confirmed in subsequent studies,[8] and Franklin[8] found that Piracetam interfered with hemoglobin S polymerization in vitro at much higher concentra-

tions than those obtained in vivo. In essence Piracetam has three possible separate simultaneous actions. It reverses sickling by disrupting the hydrophobic bonding of SS hemoglobin; it increases membrane deformability by dephosphorylating membrane proteins, thus rendering cells more resistant to lysis; finally, it reduces blood viscosity by inhibiting platelet aggregation.[12-16]

In all previous clinical trials Piracetam was found to be relatively safe and nontoxic. In our patients, aside from one subject who experienced dizziness every time she received the drug, no other side effects were reported. This particular patient was not included in the study because of poor compliance.

Although our results should be interpreted with caution, they do suggest that Piracetam may be helpful in ameliorating painful crises in SCA. In view of the safety of the drug and the absence of other safe antisickling agents at present, we feel that further well-controlled trials using a larger sample, a longer period of study, and possibly larger doses are warranted and justified.

REFERENCES

1. Guirgea C, Lefevre D, Lescrenier C, *et al.*: Pharmacological protection against hypoxia-induced amnesia in rats. *Psychopharmacologia* 20:160 1971
2. de Melo GO: Piracetam in sickle cell anaemia. *Lancet* 2 (7995):1139 1976
3. de Araujo JT, Nero GS: Piracetam and acetamide in sickle cell disease. *Lancet* 2 (8034):411 1977
4. de Araujo JT, Eloise MRJ, Dava T, *et al.*: Long-term use of Piracetam in sickle cell anemia. *Abstracts. XVIIth Congress of the International Society of Hematology*, Paris, II:463 1978
5. Skondia V, Bick RL: Prophylaxis of sickle cell vaso-occlusive crises with Piracetam. *Journess Medicales d'Abidjan* Jan. 1981, paper No 11
6. Bick RL, Skondia V, Nix K: Prophylaxis of sickle cell vaso-occlusive crises with oral Piracetam. *Blood* 58 (5) (suppl 1) 56a 1981
7. Costa FF, Zago MA, Bottura C: Effects of Piracetam and rodocetamide on erythrocyte sickling. *Lancet* 2 (8155):1302 1979
8. Franklin IM: Piracetam in sickle cell disease. *Lancet* 1 (8143):767 1980
9. Goldberg CAJ: A new method for starch gel electrophoresis of human hemoglobin with special reference to the determination of hemoglobin A2. *Clin Chem* 4:484 1958
10. Mollison PO, Veal N: The use of the isotope Cr51 as a label for red cells. *Br J Haematol* 1:62 1955
11. Read RC, Gilbertsen S: Radioactive sodium chromate and the measurement of red cell and plasma volume in man. *Arch Intern Med* 100:259 1957
12. Nalbandian RM, Henry RL: A new clinically useful chemotherapeutic agent for sickle cell disease. *Abstracts. XVIIth Congress of the International Society of Hematology*, Paris II:461 1978
13. Nalbandian RM, Henry RL: Desickling mechanism of Piracetam. *Blood* 54 (suppl):101a 1979
14. Nalbandian RM, Henry RL, Murayama M: Sickle cell diseases: two new therapeutic strategies. *Lancet* 2 (8089):570 1978
15. Bick RL: In-vivo platelet inhibition by Piracetam. *Lancet* 2 (8145):752 1979
16. Bick RL, Skondia V: Piracetam: results of a preliminary *in vivo* trial as a platelet suppressant. *Blood* 54 (suppl):234a 1979