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Clinical Efficacy of Piracetam in Treatment of Breath-Holding Spells

M. Metin Donma, MD

To evaluate the efficacy of piracetam therapy, 76 children with breath-holding spells admitted to the Outpatient Clinic of Dicle University Medical Faculty Paediatrics Department and Bakırköy State Hospital, Paediatrics Department between 1988 and 1990 and 1991 and 1996, respectively, were included in this placebo-controlled trial. Diagnosis of breath-holding spells was made for all cases by medical history, pediatric physical examination, electroencephalogram, and laboratory findings. Placebo or piracetam as suspension was administered to patients on a randomized basis; piracetam was administered to children in suspension 40 mg/kg/day in 2 divided doses for a period of 2 months. Of the 76 children enrolled, 39 received piracetam and 37 received placebo. Overall, control of breath-holding spells was observed in 92.3% of the patients in the group taking piracetam as compared with 29.7% in the group taking placebo ($P < .05$). No differences between the 2 groups in adverse events or side effects were observed. Complete blood count, biochemical profile, and urine analysis taken before and after treatment revealed no change from beginning to end and no difference between the 2 groups. It is suggested that piracetam is a safe and effective drug, with an incidence of side effects no different from that of placebo, for the treatment of breath-holding spells. **© 1998 by Elsevier Science Inc. All rights reserved.**

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Introduction

Breath-holding spells (BHS) is a type of syncope most commonly encountered in the early years of life (6 months to 3 years of age) that arises with sudden cyanosis and loss of consciousness during the expiration period of crying out [1-4].

Piracetam has a chemical structure of 2-oxo-1-pyrollidone acetamide, a molecule with close similarity to that of gamma aminobutyric acid (GABA), an inhibitory neurotransmitter [5,6]. The radioprotective effects and antiarrhythmic actions of piracetam are also explored [7,8].

In various studies performed to date in the field of pediatrics, piracetam has been used in the treatment of newborn infants [9] and in children who have the following: learning difficulties [10,11]; displays of anger, displeasure, or obstinacy, and character anomalies [12,13]; observed mental and behavioral disorders, reductions of memory, or limited memory capacity [14,15]; school failure or school problems [16,17]; low mental age or defect relevant to mental functions [18,19]; nocturnal enuresis [20-22]; Down syndrome [23]; spastic cerebral palsy [24]; or various speech disorders [25].

This study was designed to evaluate the efficacy of piracetam therapy in children with BHS demonstrated in early childhood.

Patients and Methods

Seventy-six children with BHS admitted to the Outpatient Clinics of Dicle University Medical Faculty, Paediatrics Department within a period of 2 years (between January 1988 and January 1990) and to the Ministry of Health Bakırköy State Hospital, Pediatrics Department within a period of 5 years (between July 1991 and July 1996), were included in the scope of this blind placebo-controlled study. Diagnosis of BHS was made by medical history, pediatric physical examination, electroencephalogram (EEG), and laboratory findings for all patients. The trial was a randomized comparison of piracetam suspension and a placebo suspension of similar taste and appearance. Seventy-six consecutive cases were to be enrolled, with 39 of the patients receiving piracetam suspension (40 mg/kg/day) and 37 receiving placebo on a randomized basis twice a day for 2 months.

The parents of the patients described typical symptoms of BHS. Inclusionary criteria of BHS were as follows: majority of the attacks that were believed to be of cyanotic form arose as the result of crying caused by stress, such as a sudden fright or some painful test or treatment, and

From the Ministry of Health; Bakırköy State Hospital; Clinics of Paediatrics; Bakırköy; Istanbul, Turkey.

Communications should be addressed to:
Sp. Dr. Mustafa Metin Donma; Paediatrician; 11. Kisim; MESA Villa No. 22; Ataköy; Istanbul, Turkey.
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Table 1. Characteristics of the treatment groups

	Piracetam Suspension	Placebo Suspension
No. of patients	39	37
Age (months)*		
(Mean ± SE)	14 ± 0.7	15 ± 0.6
Range	6-35	7-36
Sex*		
Male (%)	22 (56.4)	21 (56.8)
Female (%)	17 (43.6)	16 (43.2)
Age (months) at which the first episode occurred*		
(Mean ± SE)	7.9 ± 0.5	8.2 ± 0.5

* $P \geq .05$

Abbreviations:
SE = Standard error

were characterized by crying, the interruption of crying, a sudden apnea followed by a hypertonic state, and subsequent decreased muscle tone and loss of consciousness. Pallid attacks were caused by apnea that occurred after an emotional or mechanical trauma and were characterized by opisthotonos, urinary incontinence, paleness, bradycardia, and the asystole of short duration. Medical examination and neurologic evaluation of the children were normal. Full blood examinations including hematologic parameters were carried out in all patients. No finding of epilepsy has been noted in EEG. The children with symptoms of BHS who manifested epileptic electrical discharges in EEG, congenital defects, biochemical abnormalities (e.g., hypocalcemia, hypomagnesemia, hypoglycemia, and abnormal levels relevant to serum electrolytes) were not included in the scope of the study.

Piracetam was administered orally (40 mg/kg twice daily) to 30 patients without anemia for 2 months. Elementary iron, 5 mg/kg, 3 times daily, was administered to 9 children with anemia, in addition to piracetam therapy for 2 months.

The patients attended the clinic at the start of the study, after 2 months to evaluate the efficacy of piracetam and placebo on BHS, and then at 3-month intervals to assess whether the clinical symptoms of the patients were adequately alleviated by this treatment regimen.

Results

The ratio of boys to girls was 1.3:1; 43 boys and 33 girls were included in the study of 76 children with BHS. Mean age of the children was 14.5 ± 1.1 (range 6-36) months. Characteristics of the treatment groups are delineated in Table 1.

Laboratory findings related to iron-deficiency anemia were found in 9 of the 39 children receiving piracetam suspension. No findings of anemia were detected in the remaining 30 patients. Serum calcium, magnesium, glucose, and electrolytes were found to be within normal limits for all patients.

Nine patients with anemia (23%) in the piracetam group and 9 patients with anemia (24%) in the placebo group were treated with oral administration of elementary iron preparations plus piracetam and placebo, respectively. The rest of the patients in each group were treated only with oral piracetam or placebo for 2 months. In the piracetam group the mean values for hemoglobin, serum iron, total iron-binding capacity, and percent saturation were 9.1 ± 0.5 gm/dl, 36 ± 2 μg/dl, 441 ± 24 μg/dl, and 8.1 ± 0.8%, respectively. Corresponding values after completion of the therapy were found to be 13.2 ± 0.9 gm/dl, 102 ± 8 μg/dl, 332 ± 18 μg/dl, and 30.7 ± 2.5%. In the placebo group the mean values for hemoglobin, serum iron, total iron-binding capacity, and percent saturation were 9.3 ± 0.5 gm/dl, 40 ± 2 μg/dl, 450 ± 28 μg/dl, and 8.9 ± 0.8%, respectively. The corresponding values after the completion of the therapy were observed as 13.0 ± 0.8 gm/dl, 96 ± 7 μg/dl, 320 ± 16 μg/dl, and 30.0 ± 2.1%.

Table 2. Results of treatment: total number of BHS per month

	Piracetam Suspension (n = 39)	Placebo Suspension (n = 37)	*P*-Value
Before treatment	2.3 ± 0.2	2.4 ± 0.2	NS
After completion of treatment	0.8 ± 0.1	1.7 ± 0.1	<.05

Abbreviations:
BHS = breath-holding spells
NS = not significant ($P \geq .05$)

At the end of the treatment, for a period of 2 months, clinical success was 92.3% and 29.7% in the piracetam and placebo groups, respectively ($P < .05$). This was confirmed by the medical history, physical examination, pediatric neurologic evaluation, and laboratory findings. The side effect of most concern for patients taking piracetam was sleeping disorder, which was reported in 2 of 39 patients (5.1%) receiving piracetam and 1 of 37 (2.7%) receiving placebo. The other effects were mild, isolated incidents from which all recovered without therapy. Incidences of BHS according to therapy regimens and groups, as well as clinical efficacy, are shown in Tables 2 and 3, respectively. These findings support the hypothesis that piracetam provides greater control of attacks and no greater incidence of adverse effects than placebo.

Discussion

BHS is a syncope observed in early childhood; its differential diagnosis from epilepsy is required and should

Table 3. Results of treatment: clinical outcome

	Piracetam Suspension (n = 39)	Placebo Suspension (n = 37)	*P*-Value
Success* (%)	36 (92.3)	11 (29.7)	<.05
Failure† (%)	3 (7.7)	26 (70.3)	<.05

* Absence of BHS during the 6-month period after the completion of treatment for 2 months.
† One or more BHS during the 6-month period after the completion of treatment for 2 months.

Abbreviations:
BHS = Breath-holding spells

be well defined [1,3]. In our study, medical examination and pediatric neurologic evaluation of all cases were normal; no finding of epilepsy was observed in EEG. It was also reported that BHS were observed more frequently in boys than in girls [1]. Because 43 of 76 children in this study were boys, the ratio of boys to girls was 1.3:1. This correlated closely with findings reported in other articles [1,3].

If children with BHS manifest either low hemoglobin levels in blood or emotional factors, these should be treated as indicated. BHS can be a source of considerable parental anxiety and are a frequent cause of referral to pediatric services. A reduced frequency of BHS has been reported as a result of anticonvulsant therapy [26]. Anemia is known to be associated with both an increased apneic pause frequency and with cyanotic BHS. In some patients, anemia may be a factor contributing to BHS; correction of concomitant anemia may produce amelioration or remission of the spells [27,28]. In the past years, atropine or atropine-like agents have been used therapeutically in such patients, but these agents have not been recommended in anticonvulsant therapy [2-4]. In our study, 9 (23%) patients with iron deficiency anemia in piracetam group and 9 (24%) patients with iron deficiency anemia in the placebo group were treated with oral iron preparation; all have responded favorably to this therapy protocol used for 2 months. Parents of our patients were also informed of the need to remove the causative psychologic factors and to avoid precipitating acute emotional disturbances, where possible. Piracetam was administered to our patients with BHS, because no other reports on the therapy have been presented to date.

Despite a large volume of reports on various antiepileptic drugs used in various populations [29-31], relatively few studies were reported of the use of piracetam therapy in children with epilepsy [32-35]. Barbagallo et al., a study group from Italy, have performed the first wide-scope study on 169 children with epilepsy. The administration of piracetam for 30 to 360 days, in addition to antiepileptic drugs, induced significant improvement in symptoms related to perception and motor development skills [32].

This group has also reported that 33 children with epilepsy, 3 months to 4 years of age, who also showed psychomotor retardation, and 131 epileptic children with impairment in mental functions, have responded favorably to the piracetam therapy used [33,34].

Kunneke and Malan used piracetam therapy for 16 weeks along with antiepileptic drug therapy in 16 epileptic patients (8-19 years of age) with some learning difficulties, and they have reported significant improvements in the patients' difficulties in focusing attention in the classroom, their participation in class discussions, and their performances in school. Social interactions also increased [35].

The mechanism of action of piracetam has not yet been clearly explained, although some investigators consider the action of piracetam to be through the central nervous system by increasing cortical control upon subcortical field, particularly on telencephalone [21,36]. No significant side effects related to piracetam therapy were reported in our study or in literature surveyed [37-40].

Previous investigations of BHS have suggested an autonomic nervous system dysfunction, which in turn may contribute to the pathophysiology of severe BHS in children. Cerebral anoxia is the ultimate factor responsible for the loss of consciousness observed in the severe forms of BHS [41-43].

Piracetam has been reported to increase the oxygen consumption of the brain. The therapeutic monitoring of piracetam in women with fetoplacental dysfunction has suggested that it increases fetus resistance to hypoxic conditions [44,45].

Hypoxia-ischemia elicits a large increase in extracellular glutamate in vivo. Glutamate is the principal excitatory neurotransmitter in the brain, and its interactions with specific membrane receptors are responsible for many neurologic functions, including cognition, memory, movement, and sensation [46-48].

Excessive release of excitatory amino acids, such as glutamate, is associated with convulsions and neurotoxicity. Glutamate and aspartate appear to play important roles in the initiation, spread, and maintenance of epileptic activity. The link between stimulation of receptors by these amino acids and activation of nitric oxide synthases led to the suggestion that overproduction of nitric oxide might be involved in conditions such as cerebral ischemia and epilepsy. Glutamate as an excitotoxin may be responsible for the production of neurotoxic damage. The best evidence of the role excitotoxicity plays in neurologic disease is in hypoxic-ischemic brain damage [46,47,49].

Drugs that act on sodium channels and decrease the pathologic release of glutamate observed in ischemia are effective anticonvulsants in animal models and in adult and childhood syndromes of epilepsy [47].

Glutamate receptor antagonists are reported to block hypoxic-ischemic brain damage. With the development of various classes of glutamate receptor antagonists, it was demonstrated that excitotoxicity is a receptor-mediated event; antagonists can prevent both excitation and toxicity. The effect of excessive concentrations of glutamate could be antagonized at the receptor level, and drugs could be used to offset the neurotoxic events set in motion by receptor overstimulation [46,48].

Glutamate antagonists selective for *N*-methyl-D-aspartate (NMDA) or non-NMDA receptors are potent anticonvulsants. Drugs that block glutamate might prevent seizures and neural degeneration from overexcitation. Glutamate-receptor antagonists are important potentially as cerebroprotective agents to be administered directly after focal or generalized cerebral ischemia and acute head injury [47,50].

GABA is a compound that has been shown to decrease glutamate release in a variety of in vitro preparations.

GABA, acting on a presynaptic $GABA_B$ receptor, decreases glutamate release. Drugs that increase GABA function have been used to treat the excessive discharge of neurons that is epilepsy [47,50].

Piracetam is a molecule with close similarity to that of GABA, an inhibitory neurotransmitter that causes the appearance of inhibitory hyperpolarizing potentials. Piracetam also appears to act on various systems via an increase of the inhibitory hyperpolarizing processes [5,6, 51].

There appears to be a close relationship between the pathophysiologic mechanisms involved in BHS and anoxia. Information obtained from the reports based on observations that piracetam is associated with increased brain tissue oxygen consumption and its ability to increase the inhibitory hyperpolarizing processes in a manner similar to that of GABA (which has been shown to decrease excessive glutamate release caused by hypoxia/ischemia) may be introduced as the possible mechanism for the benefits piracetam brings to patients with BHS.

In this study, piracetam has been administered to patients with BHS. No study on this therapy was found in a survey of the literature. Overall, control of BHS was observed in 92.3% of patients in the group taking piracetam as compared with 29.7% in the group taking placebo for 2 months ($P < .05$). The results of this study indicate that piracetam was efficient for the treatment of children with BHS in early childhood and provided a greater relief from attacks with no greater incidence of adverse effects than placebo.

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