Clonidine Therapy for Attention Deficit Hyperactivity Disorder in Children

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Abstract

Twenty children with attention deficit hyperactivity disorder (ADHD) were recruited to evaluate the effect of clonidine administration. It was given initial-recruited dose of 3 mg/kg/day which was gradually increased weekly and divided b.d.s or t.d.s . All cases were subjected to psychometric studies: i. assessment of the activity level (the Arabic version of Conner's rating scale and ii. IQ (Stanford Binet test). Hemoglobin estimation and EEG evaluation were also done. Clonidine therapy decreased significantly the activity score with respect to pretreatment level and this score showed significant rise after clonidine withdrawal ($P<0.05$). The activity score was significantly higher in those with low hemoglobin level when compared with normal hemoglobin group. Generalized activity in EEG was detected in 55% of cases and there was not any significant relation between the presence or absence of abnormal EEG pattern and the activity score either before or after treatment. Clonidine administration is recommended mainly with children especially those who are primarily impulsive, unreflective but not for distractibility and should be combined with iron therapy in cases with a low hemoglobin level.

Introduction Attention deficit- hyperactivity disorder (ADHA) is a common psychiatric syndrome in childhood. It is most often presented with hyperactivity, inattention, impulsiveness and behavior problems that disrupt normal childhood development. (Grohan, 1991).

The etiology of ADHD remains uncertain; however, several factors have been proposed as precursors to its development. The underlying pathophysiology appears to involve biochemical defects in the neuro-transmission of catecholamines. (Mercugliano 1993).

Norepinephrine is known to enhance excitatory inputs, resulting in increase in the level of alertness and arousal and may contribute to the hyperexcitable state of ADHD patients (Santora and Hart, 1992).

A combination of non pharamacologic and pharamacologic therapy should be used. The former must include development programs that provide the basic educational and behavioral modifications as well as socialization skills (Hunt et al , 1986).

The present study was designed to evaluate the effect of clonidine as a part of pharamacologic therapy in the treatment of ADHD in children.

Material and Methods The study was conducted on 20 children who met clinical and rating scale criteria for ADHD according to the Arabic version of Conner's Parent Rating Scale. All subjects were expressed to a structured interview that included:

1. Clinical evaluation (age, sex, weight, height),initial blood pressure, relevant anti-or perinatal events and relevant past history.
2. Psychometric studies:

a. Assessment of the activity level score using "The Arabic version of Conner's Rating Scale" (El-Dafrawi et al, 1990).
b.IQ using "Stanford Binet" test. Cases with IQ less than 55 were excluded from the study.
3. Laboratory investigations:
a. Hemoglobin estimation.
b. EEG

Clonidine was given as an initial dose of 3 mg/kg/day in the evening. The dose was gradually increased weekly and divided BDS or TDS according to the Child's response or the appearance of the side effects. The maximum dose was 6 mg/kg/day . The drug was continued for 8 consecutive weeks. Re-evaluation of the children was done after complete withdrawal of the drug which was done over a duration of 2 weeks.

Results

I Clinical Findings:

The studied 20 hyperactives were 14 males and 6 females with a mean age of 5.66±1.52 years. Their weight and height percentiles lied within the normal range for their age and sex. The weight to height ratio for all studied children showed that there is evidence of malnutrition. The mean systolic blood pressure at the initial visit was 105.5±9.445 and the mean diastolic blood pressure was 71.00±-6.407 (Table I).

School grading of the studied cases: Six of the children were enrolled into elementary schools : two in the first grade, 3 in the second and one in the third. Three were in kindergarden. Five were not enrolled in any educational services and 6 were dismissed of their kinder garden because of their disturbing behavior. The mean IQ value for all children included was 73.4±12.51.

Response to Clonidine Therapy

The cases were assessed using the "Arabic version of Conner's scale" before, during and after clonidine therapy. The mean score of behavior rating had diminished significantly after clonidine administration when compared with its mean pretreatment value ($P<0.05$). After clonidine withdrawal , however, the mean score showed significant rise over its mean values during active clonidine administration (Table II).

Blood Pressure changes after Clonidine Therapy

There was a significant reduction in the systolic blood pressure during all follow up visits when compared with its initial value ($P<0.05$). As regards the diastolic blood pressure, there was no significant reduction in its values during follow up from its basic value of initial visit ($P<0.05$).

II Laboratory Changes:

A. Hemoglobin percentage:
Seventy percent of the studied children had normal hemoglobin level(mean hemoglobin level 11.25 gm%) while only 30% had low hemoglobin level (9.1gm%).

Table III shows that before clonidine the mean score level was significantly higher in those with a low hemoglobin level when compared with a normal hemoglobin group. After clonidine and iron therapy. However, the difference between the two means was statistically insignificant.

B. EEG:
There was generalized activity in the EEG of 55% of cases. Table IV shows that there was no significant difference in the mean score level whether before or after treatment between those with normal EEG and those with generalized activity.

Table I Clinical data of studied children

Cases	age/ys	sex	wt%	ht%	wt/ht	initial blood pressure		relevant peri-natal	relevant past history
						systolic	diastolic		
1	5 5/12	M	20	20	0.95	90	60	-	delayed talking
2	6	M	30	60	0.97	100	70	-	delayed talking
3	4	F	95	40	0.97	100	70	-	delayed talking
4	8	F	70	50	0.96	110	70	-	head trauma
5	7.5	M	50	70	0.95	110	70	-	meningitis
6	4.5	F	10	20	0.95	100	60	toxemia	delayed talking
7	4	M	70	30	0.98	90	70	-	delayed talking
8	5	F	97	30	0.98	110	80	-	-
9	58/1 2	M	20	40	095	100	60	-	delayed talking
10	5.5	F	30	80	0.96	120	70	-	-
11	59/12	M	30	80	0.99	110	70	-	-
12	5	M	80	20	0.97	110	80	-	delayed talking
13	4.5	M	70	40	0.95	110	70	-	delayed talking
14	8	M	50	80	0.98	100	70	-	-
15	9	M	90	60	0.99	110	80	-	delayed talking
16	4	M	20	30	1.00	110	70	pre-maturity	-
17	59/12	M	50	50	0.96	90	70	-	delayed talking
18	65/12	M	20	40	1.00	100	70	-	delayed talking
19	5	M	30	60	0.97	110	70	-	-
20	5.5	F	50	30	0.99	100	80	-	-

Table II The mean score of the" Arabic version of Conner's Rating Scale" before and after clonidine therapy

Response to clonidine	Score of the" Arabic version of Conner's Rating Scale"		
	before clonidine	during clonidine intake	after clonidine withdrawal
Good response	Range :18-26 Mean :21	Range: 8-25 Mean: 9.9	Range: 17-23 Mean :20.1
Mild response	Range :23-26 Mean :24.7	Range:16-19 Mean: 9.9	Range: 20-24 Mean :22
Poor response	Range :17-23 Mean :20.2	Range: 16-23 Mean: 19.2	Range: 16-22 Mean :19.7

Paired "t" value between the score level before and after clonindine=8.34***
Paired "t" value between the score level during treatment and after withdrawal= 8.21*

Table III: Effect of Hb level on score level before and after clonidine adminstration

Score level	Normal Hb level			Low Hb level			" t"
	no	mean	± SD	no	mean	± SD	
Before	14	20.79	1.54	6	24.0	2.28	3.6987**
After	14	10.93	4.22	6	12.5	4.28	0.7584

Table IV Comparison between score level before and after treatment and presence or absence of EEG changes

Score level	Normal EEG			Abnormal EEG			" t"
	no	mean	± SD	no	mean	± SD	
Before treatment	9	21	± 3.16	11	22	± 3.32	0.684
After treatment	9	21.6	± 6.02	11	3.71	± 3.32	0.4723

Discussion Clonidine is an antihypertensive agent that exerts its action on presynaptic neurons to inhibit the release of norepinephrine (Santro and Hart, 1992).

The aim of this study was to evaluate the effect of clonidine therapy in ADHD children. Thus clinical, psychometric and laboratory assessment were applied to 20 children suffering from this condition.

The Conner's Parent Rating Scale demonstrated a significant reduction in the mean score level of hyperactivity after clonidine administration. 60 %of the studied children showed total improvement, 20 % showed mild but not complete improvement, and another 20% showed no significant improvement in their behavioral rating during treatment. These results are in agreement with those of other investigators (Hunt et al,1986; Hunt et al ,1985; Raskin et al,1984).The mean systolic blood pressure was significantly lower during clonidine therapy. However, there were no subjective symptoms and its values were still within the normal range for age and sex.

As regards hemoglobin level, it was evident that low hemoglobin level was associated with a higher degree of hyperactivity, irritability, restlessness and decreased attentiveness in those children. This can be further supported by the work of Oski et al.(1978; Deinord et al,(1986); Lozoff et al,(1987), who reported that iron deficient children appear to be more disruptive, irritable, restless and less attentive than a similar group of children who were not iron deficient.

Thee biochemical link between iron deficiency and psychological function is suggested to be related to abnormal catecholamine metabolism where monoamine oxidase enzyme which deaminate norepinephrine and other amines, needs iron during its activity (Millichap and Goldrey, 1967).

In this work, EEG done for the studied children reveals abnormal patterns in 55% of cases in the form of generalized activity. These results are supported by the work of Kenny et al.(1971); Shaywitz and Shawtiz, (1984), who reported that non specific EEG abnormalities are evident in half of the affected ADHD children. This study did not reveal any significant relation between the presence and absence of abnormal EEG patterns and the level of hyperactivity in children either before or after treatment.

The most common side effects of clonidine therapy were excessive sleepiness(80% of cases) and anorexia(35%). These transient symptoms were apparent only during the first few weeks of clonidine adminstration.

While the main effect of clonidine is to increase calmness and frustration tolerance but not diminish distractibility, the main effect of methyl phenidate (MPH) is to focus attention. A combination of clonidine with `MPH in the treatment of children with ADHD may give better results of improvement and permits a much lower dose of MPH with little effects especially with those whose symptoms are more difficult to control or those who have only partial response to clonidine alone.

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أستعمال عقار الكلونيدين كعلاج لخلل نقص الأنتباه و النشاط الزائد لدى الاطفال

تم اختيار عشرين طفلا ممن يعانون من خلل نقص الأنتباه و النشاط الزائد. و ذلك لتقويم أثر استعمال عقار الكلونيدين. و قد أعطى العقار فى جرعة مبدئية ٣ ميكروجرام لكل كجم من وزن الجسم فى اليوم. وتم زيادة الجرعة بالتدريج اسبوعيا. و قد شمل البحث:(١) تقديم مستوى النشاط باستخدام النسخة العربية من مقياس كونز (٢) اختبار ستانفورد بينيه للذكاء.

و قد اظهرت النتائج أن استخدام الكلونيدين قد قلل بدرجة ملحوظة درجة النشاط بالمقارنه الى فترة ما قبل الاستخدام كما ان هذا النشاط زاد بدرجه ملحوظه ايضا بعد توقف استخدام العقار . ($P < 0.5$) و كانت درجة النشاط اعلى لدي الاطفال ذوي مستوى الهيموجلوبين المنخفض (الانيميا) مقارنة باصحاب المستوى العادى. و لم تلاحظ اى فروق ذات دلاله بين وجود او عدم وجود انماط معينه في رسم المخ الكهربائى وبين درجة النشاط سواء بعد او قبل العلاج.

و يستخلص من ذلك اننا نوصى باستخدام الكلونيدين اساسا مع الاطفال خاصة اولئك الذين يظهرون اندفاعيه و عدم تبصر و لا نوصى فى حالة تشتت الانتباه كما انه يجب اضافة مركبات الحديد فى الحالات التي تعانى من الانيميا.

Principles of Drug Treatment in Chronic Elilepsy:

Choice of drugs made according to seizure type and previous treatment history.

Treat with one or a maximum of two anticonvulsants. There is no placeacdfor therapy with more than two drugs

Choice of dosage should be that which produces the maximum seizure reductione with out toxicity.

Recognize that there are limits to drug therapy, and that some patients' seizures are intractable to currently available drugs.

Do not overtreat. Gaurd against drug toxicity.

Avoid sedative drugs unless they confer definite benifit.

Drug changes should be made sloely and patients should be aware that there may be a transient exacerbation of seizures during the change-over period.

Ciba Geigy