Arq Neuropsiquiatr 2002;60(2-B):374-377

COMPARISON OF THE EFFICACY OF CARBAMAZEPINE, HALOPERIDOL AND VALPROIC ACID IN THE TREATMENT OF CHILDREN WITH SYDENHAM´S CHOREA

Clinical follow-up of 18 patients

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ABSTRACT - In order to compare and contrast the efficacy of haloperidol, carbamazepine, and valproic acid in the treatment of Sydenham´s chorea a prospective study including 18 cases of this disorder was undertaken. Age of patients ranged from 7 to 15 years. Ten children were female and 8 were male. All but one had generalized, either symmetric or asymmetric chorea. The patients were divided in three equal groups, and were given a standardized dose of each of the drugs built-up over a week. Following therapy, the six children receiving valproic acid showed remarkable improvement, without side effects. Five patients receiving carbamazepine showed improvement without side effects. Only three of the patients that received haloperidol improved. In the 4 cases that did not show clinical improvement after one week of treatment, therapy with valproic acid led to disappearance of the symptoms in a lapse that ranged from 4 to 7 days. Recurrence related to discontinuation of treatment was observed in two patients. In view of the present results we recommend valproic acid as the first choice drug to treat Sydenham chorea.

KEY WORDS: Sydenham´s chorea, carbamazepine, haloperidol, valproic acid.

Comparación de la eficacia de carbamazepina, haloperidol y acido valproico en el tratamiento de niños con corea de Sydenham: seguimiento clínico de 18 pacientes

RESUMEN - A fin de comparar y contrastar la eficacia de haloperidol, carbamazepina y ácido valproico en el tratamiento de la corea de Sydenham, se realizó un estudio prospectivo que incluyó 18 casos de esta patología. La edad de los pacientes varió de 7 a 15 años. Diez de los niños eran varones y el resto hembras. A excepción de uno de ellos, todos tenían corea generalizada, simétrica ó asimétrica. Los pacientes fueron divididos en tres grupos iguales, a cada uno de los cuales se le administró una dosis estandarizada de los medicamentos mencionados durante una semana. Luego del tratamiento, los seis pacientes que recibieron ácido valproico mostraron mejoría notable sin efectos colaterales. Cinco de los seis pacientes que recibieron carbamazepina exhibieron mejoría sin efectos colaterales. Solo tres de los pacientes que recibieron haloperidol mejoraron. En los cuatro casos que luego de recibir estas dos últimas drogas sin experimentar mejoría clínica luego de una semana, se instaló terapia con ácido valproico, lo que llevó a desaparición de la sintomatología en un lapso de 4 a 7 días. Se observó recaída relacionada con tratamiento discontinuado en dos de los pacientes. A la vista de nuestros resultados, recomendamos el ácido valproico como droga de primera elección en el tratamiento de la corea de Sydenham.

PALABRAS CLAVE: corea de Sydenham, acido valproico, carbamazepina, haloperidol.

Sydenham´s chorea (SC) is the most prevalent form of acquired chorea, and it constitutes a major manifestation of rheumatic fever[1]. Thomas Sydenham originally described this ailment in 1866. Involuntary movements, lack of motor coordination and emotional instability characterize it[2]. In a remarkable number of cases the disease is self-limited, hence bed rest in a quiet environment, and stress avoidance may suffice. However, in patients with moderate or severe movement disorders, the accompany-

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Received 21 September 2001, received in final form 7 December 2001. Accepted 12 December 2001.

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ing anxiety, obsessive-compulsive signs, and other associated psychological dysfunction may prevent daily activities and brings into consideration therapy with specific medication, in spite of the fact that most of such drugs have side effects that limit their use. An impressive list of therapeutic options has been used to treat this disorder: ketogenic diet, amphetamines, steroids, haloperidol (HP), valproic acid (VPA), carbamazepine (CBZ), reserpine, chlorpromazine, and phenobarbital[3-5]. Many reports confirm the efficacy of HP, CBZ and VPA in uncontrolled studies[6-11], and only a few controlled investigations compare the efficacy and side effects of currently used medications. A recent prospective study that included 10 children with chorea suggests that CBZ may prove useful as the drug of choice for the treatment of rheumatic chorea[12]. In another recent trial that compared HP and sodium valproate in a series of 24 patients, the percentage of individuals that responded to treatment was significantly higher in the HP group[13].

The purpose of the present investigation is to compare and contrast the efficacy of HP, CBZ, and VPA in the treatment of SC in a series of 18 patients through the analysis of clinical and laboratory findings, clinical course, and side effects related to these drugs.

METHOD

The study group included 32 patients with SC that were referred to the Pediatric Neurology department of the University Hospital of Maracaibo, Venezuela during the period January 1st. 1995 – December 31, 1999. Patient selection was based on the following criteria: a) clinical findings consistent with the diagnosis of SC, such as abnormal movements and emotional liability; b) clinical course of less than 4 weeks; c) no previous history of choreic episodes; d) no previous history of treatment with other drugs. Fourteen patients were excluded from the trial because they failed to meet the required selection parameters. The symptoms recorded in the remaining 18 cases were classified as mild, moderate or severe according to the criteria established by Aron et al.[14]. The study protocol included a complete clinical history with detailed information regarding family history, form of presentation, signs and symptoms, clinical course, duration, associated manifestations. Laboratory tests included hemogram, liver function, antistreptolysin O and streptozyme titers, erythrocyte sedimentation, reactive C-protein, LE cells, antinuclear antibodies, complement, anticardiolipin antibodies; electrocardiography, electroencephalography and neuroimaging. The type of treatment was decided randomly according to the order of admission to the hospital. Six patients were treated with haloperidol at a dose of 3 mg/day, b. i. d.; 6 patients were assigned to the valproic acid group (20 mg/kg/day, b.i.d.), and the remaining 6 patients were given carbamazepine (15-20 mg/kg/day, b.i.d.).

The response to treatment was assessed by the clinical course and daily neurological evaluation. Each drug was maintained for at least a week, and the efficacy or failure of the treatment with each of the drugs was determined by the disappearance of the symptomatology as assessed by the visual scale. In case of failed response, the medication of first choice was discontinued and treatment with a different drug was installed. No treatment withdrawal occurred during the study period.

The study was authorized to be carried out by the Ethics Committee of the University Hospital.

RESULTS

Clinical and ancillary findings

Ten females and eight males, aged 7-15 years were included in the study. None of the patients had family history of SC. Abnormal movements were generalized, either symmetric or asymmetric in 17 cases and unilateral in one case. The distribution of the cases according to the different abnormal movements observed upon admission is displayed in Table 1. As shown in Table 2, in addition to the choreic movements other clinical manifestations that were readily evident, included emotional instability, gait

Table 1. Type of abnormal movements in 18 cases of Sydenham´s chorea studied.

Type of dyskinesia	n	%
Generalized, asymmetric	10	55.5
Generalized, symmetric	5	27.7
Unilateral	1	5.5
Choreiform status	1	5.5
Chorea mollis	1	5.5

Table 2. Associated neurological manifestations in 18 patients with Sydenham´s chorea studied.

Neurological symptom	n	%
Behavior alterations	13	72.2
Gait disturbance	10	55.5
Motor agitation	10	55.5
Reflex abnormalities	8	44.4
Dysarthria	7	38.8
Weakness	3	16.6

disturbances, motor agitation, abnormal reflexes, dysarthria, and generalized weakness. Three patients developed mitral valve insufficiency. Sptreptozyme values were increased in 10 patients (55.5 %). Increased antistreptolysin -O (ASO) titers were found in 7 patients (38.8%). Both increased erythrocyte sedimentation rate and positive reactive C-protein were evident in 3 cases (16.6%) LE cells, antinuclear and anticardiolipin antibodies were negative in all cases. EEG was abnormal in 7 patients (38.8%) It displayed slow and intermittent delta waves in the parieto-occipital region after eye closure. This was observed during the first two weeks of the clinical course, and disappeared 4-8 weeks later. Neuroimaging revealed no abnormalities.

Response to treatment

Complete recovery was observed in five of the patients treated with VPA following 5 days of treatment, whereas moderate improvement was recorded in the remaining case. Full recovery was achieved in five of the six patients treated with CBZ, three of these cases recovered after 5 days of treatment, whereas the other two required of treatment during 7 days before disappearance of symptoms was observed. The remaining case failed to improve. No side effects due to VPA o CBZ were documented. Three of the six patients treated with HP showed improvement following 5 days of treatment, two of these had treatment related side effects: one patient displayed excessive somnolence, whereas the other one had a dystonic reaction. Medication administration was interrupted in the four patients that failed to improve, and treatment with VPA was started. One week later these patients were symptom-free.

The duration of treatment varied from 1 to 14 months. Follow-up ranged from 10 months to 3 years. Recurrence was documented in two patients at 3 and 10 months of therapy, respectively; one of these patients had received CBZ, and the other HP. Reinstallation of therapy with VPA was followed by improvement. This drug was administered during 6 and 10 months, respectively.

DISCUSSION

SC is a movement disorder that affects patients aged 5 to 15 years, with a peak incidence at 8 years, and a 2:1 female predominance[15]. The neurological manifestations are usually preceded by emotional instability, low scholar achievement and motor clumsiness. The involuntary movements that characterize this ailment are jerky, uncoordinated, brief, generalized though predominantly asymmetric, and involve the hands, arms, and to a lesser degree the neck, face and tongue. These motor alterations appear when the patient is at rest, and may cease during sleep. A genetic predisposition to develop CS has been suggested[14-16].

As stated above, in addition to the movement disorders these patients present with assorted behavioral problems that include emotional instability, mood changes and depression. Thus, the condition may be misdiagnosed as an ailment of psychological origin.

Several studies have stressed an antecedent of streptococcal infection in up to 60% of the cases[17]. In the present series we could not demonstrate a history of streptococcal infection, or physical signs suggestive of such. Conversely, we found significant alterations in serologic tests, especially the ASO test that was elevated in 38.8% of the cases. Previous studies have signaled that up to 25% of cases of SC reveal normal ASO values[18,19]. This contrasts with acute rheumatic fever, which consistently displays increased ASO titers. The increment observed in the former usually appears early during the course of the infection and diminishes rapidly before the clinical signs of chorea develop. Comparatively, the streptozyme test appears to be more sensible than other bacterial antigens. This test defines antibodies to five streptococcal exo-enzymes, including streptolysine-O, and its titers remain elevated for several weeks. Other studies have signaled the value of anti-DNAase B and anti DNAase test in the diagnosis of SC, with increased titers in 63% of the patients up to 6 months after the onset of symptoms[20]. The variability in the results of the serologic tests may occur as a consequence of differences among the streptococcal strains, or they may be secondary to the presence of other precipitants[21,22]. The diagnosis of SC is based on the clinical examination, and the elimination of other causes of chorea. Most of changes observed in the EEG are transient, and they rapidly disappear in a matter of weeks. Neuroimaging is usually unremarkable[22-25].

The pathogenesis of SC is related to a biochemical dysfunction of the corpus striatum in response to a streptococcal infection[26-28]. The abnormal balance between the dopaminergic and cholinergic systems that determines dopaminergic hyperactivity has been pointed out as the main mechanism underlying SC. Thus, therapy is aimed at re-establishing that balance[8,9].

The clinical course of patients with SC treated with several drugs follows a path that leads to the pro-

gressive disappearance of the symptoms. Sedatives, dopaminergic receptor antagonists, and other drugs reduce the time of convalescence of the patients that harbor this disorder, with varying degrees of success. HP, a dopamine receptor blocker, has been used to treat SC, although this drug is frequently associated with side effects such as parkinsonism and dystonia[29]. Cuellar et al.[13] reported the successful use of HP as compared to VP in a group of 24 patients with SC. A dose of 0.05-0.1 mg/kg/day, b.i.d. was administered. The onset of symptoms preceded the hospital admission ranging from 1 to 30 days in 15 patients, and in more than 30 days in 9 cases. Authors that have used VPA or sodium valproate in SC reported similar results as those obtained with HP, with less adverse effects, notwithstandingly[5,11,30]. The mechanism through which VP improves chorea is related to an increase in the glutamic acid decarboxylase activity and the inhibition of GABA transaminase, which determines an elevation of brain GABA levels[5,30].

Other authors have recently reported the beneficial effect of CBZ in patients with SC. It is not well known how CBZ works in CS. A possible blockade of the dopaminergic postsynaptic receptors and stimulation of the cholinergic pathways has been hypothesized[8,9].

The three groups of patients that constituted the present series displayed clinical symptoms of 2–3 weeks duration, without evidence of spontaneous recovery before the beginning of treatment. The number of patients that responded to treatment at the end of the first week was discreetly higher in the group that received VPA. In addition, the time to improvement was significantly shorter in this group as compared to both the HP and CBZ groups.

Our results indicate that VPA is both effective and safe because of its low effective dose, and rapid response. Nevertheless, we are aware that the disparity among the different studies that have been performed to test the efficacy of a particular drug is related to several issues. Thus, other multicentric and comparative studies involving more patients are mandatory in order to answer the question of which drug is best for each particular child affected by SC.

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