EFFECTIVENESS OF BACLOFEN IN SCHIZOPHRENIA

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Administering Baclofen, a psychotropic drug in daily doses of 5 mg to 45 mg for 3 to 11 weeks to 10 cases of schizophrenia whose duration of illness is 5.4 years on the average, we made observations on the clinical course.

As to therapeutic effects, symptoms remained unchanged in nine cases and became aggravated in one case.

Electroencephalographic examinations showed no tendency to improvement.

Discussion in reference to literature was held on the relationship between GABA and the DA metabolism and also application of Baclofen to schizophrenia.

INTRODUCTION

It is well known that GABA (gamma-amino butyric acid) plays an important role in the metabolism of amino acid in the brain, but its physiological function has not yet been elucidated fully. However, it is reported that GABA and its derivatives are acting as a transmitter to the CNS inhibitory system (Purpura et al, 1975; Iwama and Jasper, 1975; Grundfest, 1966).

An attempt to raise this inhibitory function by administering GABA from outside had been made in the past. However, GABA itself does not pass through the blood-brain barrier, and therefore, GABA derivatives that pass through the blood-brain barrier were

synthesized; one of them is Baclofen (β -(aminomethyl)-p-chlorohydrocinnamic acid).

Used as a remedy for disease of cerebral and spinal spasticity clinically, it is confirmed to have an antispastic effect.

Recently, a gabaminergic hypothesis that GABA might take part in the etiology of schizophrenia has been advocated (Roberts, 1972), and attention is being focussed on the relationship between GABA and the metabolism of other amines in the brain as well as the relationship between GABA and the psychological functions.

Recently, Baclofen was administered to patient with chronic schizophrenia with favorable results (Frederiksen,

1975). Having had an opportunity to use Baclofen, the authors also have administered it to 10 cases of schizophrenia and made observations on the clinical symptoms and changes in electroencephalograms, the results of which are reported hereunder.

SUBJECTS AND METHODS

Selected as the subjects are 5 patients with schizophrenia in the Kai Hospital and 5 patients with schizophrenia in the Department of Psychiatry, Kurume University Hospital (see Table 1). Aged

17 to 46 years (averaging 28 years), they comprise 6 male and 4 female cases.

The duration of illness ranges from 8 months to 13 years (averaging 5.4 years); as major mental symptoms, mention is made of loss of contact, hypobulia, hallucination and delusion. Psychotropic agents, anti-Parkinson's disease agents and sleep-inducing agents used as basal drugs were the ones which had so far been used and these were administered as usual.

To patients in the Kai Hospital, Baclofen was administered continually for three weeks by increasing the dosage

TABLE 1

Case	Sex	Age	Duration of illness	Main symptoms	Therapeutic effects
1	Male	23	3 years, 6 months	Tension, loss of contact, hypobulia, autism	Unchanged
2	Male	17	1 year	Abulia, indifference, loss of contact, disturbance of thought process	Unchanged
3	Female	27	4 years, 9 months	Anxiety, tension, disturbance of thought process, hallucination, delusion	Unchanged
4	Female	24	8 months	Abulia, silly smile, loss of contact, apathy, auditory hallucination, delusion of persecution, autism, hypobulia	Unchanged
5	Female	26	3 years, 10 months	Anxiety, tension, auditory hallucination, hypobulia, autism	Unchanged
6	Male	28	11 years	Apathy, autism, abulia, mild negativism at times, echosymptom, disturbance of thought process	Unchanged
7	Male	27	7 years	Apathy, disturbance of thought process, wandering	Unchanged
8	Female	40	8 years	Autism, delusion, auditory hallucination, apathy	Aggravated
9	Male	22	8 months	Lowering of spontaneity	Unchanged
10	Male	46	13 years	Autism, auditory hallucination, abulia, expressionless	Unchanged

while making observations on the clinical course with 10 mg/day (2 tablets of 5 mg tab. to be taken after breakfast and lunch) for the initial week, 15 mg/day (3 tablets to be taken t.i.d. after meal) for the subsequent one week and 30 mg/day (6 tablets to be taken t.i.d. after meal) for the last week.

To patients in the Kurume University Hospital, Baclofen, 5-45 mg was administered suitably for 4 to 11 weeks.

Regarding the changes in the clinical symptoms, changes in mental symptoms and behavior were evaluated and scored by means of a form for judgement on the effectiveness hitherto in use every week before and after administration of Baclofen.

For patients in the Kai Hospital, EEG was recorded every week before the treatment and after initiation of the treatment. Nihon Kohden-make Model ME-135 13 channel was used as an apparatus for recording EEG. The amplitude was set so that pen deflections of 50 μ V 5 mm be generated; time constant was set as 0.3 seconds and the paper feeding speed as 3 cm per second. Electrodes used were of the rubber bandfixed type and arranged according to the 10/20 system.

Nihon Kohden-made Model MAF 5 was used as an automatic frequency analyzer. Being a standard type analyzer, this apparatus has five bands, namely, delta (2-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta 1 (13-20 Hz) and beta 2 (20-30 Hz). The site of analysis is Pz-A₂ and Oz-A₂, the analysis time being 5 epochs (for 50 seconds). The incidence of each frequency band is expressed in percentage of energy (percentage of the square of amplitude for each band to the sum total of square of amplitude for all bands was found). EEG was not recorded for patients in the Kurume University Hospital.

RESULTS

As shown in Tables 1 and 2, there was little change in the therapeutic effect and electroencephalogram. Regarding the therapeutic effect, symptoms remained unchanged in nine cases and were aggravated in one case.

Insomnia was seen several days after administration in one case (No. 3), but it is one which was observed at times even before administration of Baclofen, and whether it is insomnia caused by administration of Baclofen is doubtful.

As to changes in EEG, the mean value of the incidence of each band in 5 cases is shown in Fig. 1. As illustrated, there were observed a gradual decrease in the alpha band and gradual increase in the theta band both in the parietal region and occipital region after administration of Baclofen. Such a tendency was seen with an increase in dosage particularly in the occipital region. In the parietal region, the alpha band remained almost unchanged and a decrease in the theta band was observed in the first week after administration, but the theta band increased again and a decrease in the alpha band was noted three weeks after.

Regarding changes in EEG for each of the five cases, illustration is omitted here but the outline is as shown in Table 2. That is, No. 1 and No. 3 showed a slight increase in the alpha band in the first week (second week too in No. 3), but there were observed a decrease in the alpha band and an increase in the theta band from the second week down-ward. No. 2 showed a decrease in the alpha band in both regions after administration. In No. 4, the alpha band was predominant in the occipital region and the theta band predominant in the parietal region before administration, but the theta band became predominant in the occipital

region too after administration. No. 5 showed a high incidence of the delta and theta bands since before administration and it showed little change and was of the slow-wave-predominant type even after administration.

As described above, improvement in EEG was not observed in all of the five cases. Rather, there was noted a tendency for the alpha band to decrease and for the theta band to increase with an increase in the dosage.

Fig. 1

TABLE 2

Case	Changes in electroencephalogram
1. Only after 1st week	: A slight increase in alpha band ; a decrease in theta band
2. After 2nd, 3rd week	: A decrease in alpha band ; gradual increase in theta band
3. 1st, 2nd week	: A slight increase in alpha and theta band
3rd week	: A decrease in alpha band ; a decrease in theta band
4.	An increase in theta band (particularly remarkable in the occipital region)
5.	Hardly changed from the pretreatment pattern delta and theta bands predominant

DISCUSSION

The present study concerns a clinical trial we performed using Baclofen (β -(aminomethyl)-*p*-chlorohydro cinnamic acid), a derivative of GABA, one of the neurotransmitters.

GABA is said to suppress synaptic transmission in the central nervous system. GABA is produced by decarboxylation from glutamic acid; this catalysis is taken part in by L-glutamic acid decarboxylase (GAD), while co-enzyme is Plp (pyridoxal phosphate) (Holz and Palm, 1964). GABA is further subjected to β -oxidation to become gamma-amino- β -hydroxy butyric acid (GABOB).

Some mention GABA and others GABOB as a compound that exerts an action as an inhibitory transmitter in the central nervous system; thus, biochemical and physiological elucidation on the GABA group is not satisfactory yet (Roberts and Kuriyama, 1968).

Comparison of the GABA content in the brain with other amines (dopamine, norepinephrine, serotonin) shows that the GABA content is overwhelmingly large (Roberts, 1972).

A hypothesis that GABA might take part in etiology of schizophrenia, the so-called gabaminergic hypothesis was advocated (Roberts, 1972). According to this hypothesis, the inhibitory effect of GABA is lower in schizophrenia than in normal persons for one reason or another, which causes an unbalance with monoaminergic neuron and subsequently the patients present physical and mental symptoms.

Previously, studies were made of the influence of GABA-like compound gamma-hydroxy butyrate and its precursor gamma-butyrolactone or gamma-hydroxy-3 amino pyrrolidon-2 on the dopamine metabolism (Gessa et al., 1968; Walters, 1973); these GABA-like com-

pounds were said to increase DA in the brain.

It is said that psychotropic drugs represented by chlorpromazine increase DA turnover in a compensatory manner by blocking the receptor of dopaminergic neuron. Recent studies (Lahti et al., 1973) have shown that an increase in intra-cerebral GABA caused by pre-treatment with AOAA (amino oxyacetic acid, GABA metabolism inhibitory agent) is antagonistic to the effects of chlorpromazine and morphine on the DA turnover, suggesting the antagonistic action of the gabaminergic system on the dopaminergic pathway.

Regarding Baclofen used in the present study, it was reported (Fuxe et al., 1975) that an increase in DA turnover produced by administration of pimozide (having a dopaminergic receptor inhibitory action) is eliminated by administration of Baclofen, thus showing that Baclofen is similar in effect to AOAA to some extent.

Pointing out that this antagonistic effect of Baclofen on the DA metabolism is shown in DA neuron of the mesencephalic limbic system rather than the neostriatum, it was surmised that GABA might be adjusted to a change in the DA metabolism caused by psychotropic drugs in this region and it was stated that the dosage of psychotropic drugs could possibly be reduced by combinational use of GABA derivatives, if the action of psychotropic drugs is brought into play by inhibition of DA receptor in the limbic system (Fuxe et al., 1975).

Accordingly, a report that Baclofen was administered to 13 patients with chronic schizophrenia very effectively (Frederiksen, 1975) was of great interest clinically. According to this report, the effectiveness manifested itself in several days after administration of Baclofen, with autism first of all

and then insight into mental symptoms and hallucination improved; and, the course of improvement is reported in detail for one female patient.

In the clinical trial conducted later, however, therapeutic effects of this preparation were not too good, with nine cases aggravated, two unchanged and only one improved slightly (Simpson et al., 1976).

In the present study too, symptoms remained almost unchanged with regard to therapeutic effects for the ten cases covered. Electroencephalographic observations revealed no tendency to improvement. Whether or not the mechanism of action of Baclofen is identical with that of GABA is also questionable.

We have recently found that Baclofen exerts no noticeable influence on the receptor of cat primary sensory nerve cell that reacts specifically to GABA (not published yet).

Be that as it may, studies on the relationship between GABA or GABA-like compound and the DA metabolism and relationship between these compounds and mental function would serve as a clue to elucidation of etiology of schizophrenia.

We would like to continue making further studies on this subject in the future.

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