

## Antipsychotic and Prophylactic Effects of Acetazolamide (Diamox) on Atypical Psychosis

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**Abstract:** We investigated the antipsychotic and prophylactic effects of acetazolamide (Diamox) on atypical psychosis. Acetazolamide was given to 30 patients: Type I, puberal periodic psychosis, a psychosis whose onset occurs during the period of puberty and which appears repetitively with psychosis-like condition at about the same interval as the menstrual cycle (6 cases); Type II, a) presenile atypical psychosis which initially appears in patients in their 20s or 30s accompanied by manic-depressive cycles and shows acute confusional and dreamy states in the presenile period, incurable cases (7), b) atypical psychosis, in the narrow sense, cases which show acute hallucination, delusion, confusional and dreamy states accompanied by affective symptoms (8 cases); Type III, repetitively the atypical manic and depressive states, and atypical manic-depressive psychosis, and transient changes in consciousness, refractory cases (2); Type IV, atypical schizophrenia, which is considered to be schizophrenic disorders (7 cases). Among these cases, some extent of the therapeutic effects of acetazolamide (500–1,000 mg/day) was obtained in about 70%. The high therapeutic effects were particularly observed in Types I, II and III. It was less effective against atypical schizophrenia. Acetazolamide showed the effectiveness in 10 cases out of 13 cases to which lithium carbonate and carbamazepine were ineffective. The high therapeutic effects of acetazolamide were shown in the cases whose symptoms were aggravated at the interval of the menstrual cycle. No correlation was observed between the electroencephalographic abnormalities and the therapeutic effects. In addition, the prophylactic effects of acetazolamide on the periodic crisis were observed in 9 cases. From these results, acetazolamide was considered to have the antipsychotic and prophylactic effects on atypical psychosis. Since side effects due to acetazolamide were rarely observed, the present drug was considered to have a high safety margin.

**Key Words:** *acetazolamide (Diamox), antipsychotic effects, atypical psychosis*

## INTRODUCTION

In the patients with atypical psychosis, remission and recurrence appear repeatedly; thus, the social life of the patients is markedly disturbed. Although many reports have been published on the therapy of atypical psychosis, the standard therapeutic method has not yet been established. The present authors<sup>1-10</sup> have applied a carbonic anhydrase inhibitor, acetazolamide (Diamox), to the patients with atypical psychosis, and investigated its antipsychotic and prophylactic effects for several years. Although a part of this study had already been reported elsewhere,<sup>10</sup> the application of the present agent to atypical psychosis will be reported herein, including the results of the therapeutic studies conducted thereafter. No reports have been published on the therapy of atypical psychosis by applying the present agent both in Japan and abroad.

## METHODS

A clinical definition of atypical psychosis has not yet been well established. Therefore, the present authors have selected the patients to be given acetazolamide, taking their ages, clinical symptoms, courses and their physiological and biochemical findings into consideration.

In addition, meetings were held twice a year to clinically discuss the cases administered with acetazolamide; at these meetings, we discussed whether a certain case was properly judged to be atypical psychosis and on the judgment of the therapeutic effects of acetazolamide. Since the patients with the present psychosis often show the mixed symptoms of schizophrenia and manic-depressive psychosis, we have set up a special protocol for evaluating the clinical effect of

the agent. As a result of the discussion at the meetings on the severity of the symptoms before and after therapy, it was decided to classify the therapeutic effects into four degrees—markedly effective, effective, slightly effective and ineffective. Markedly effective: cases which showed a marked improvement of the psychotic symptoms accompanied by the inhibition of periodicity after the administration of acetazolamide. Effective: cases which showed an improvement of the psychotic symptoms and the prophylactic effect to a considerable extent after the administration of acetazolamide. Slightly effective: cases which showed a partial reduction of the psychotic symptoms after the administration of acetazolamide. Unchanged (ineffective): cases which showed no changes in the symptoms after the administration of acetazolamide. Since strong anxiety and excitement were observed frequently during the morbid phase of atypical psychosis, a single application of acetazolamide without concomitant drugs was difficult to be adopted. Therefore, concomitant administrations of low doses of antipsychotic drugs were applied in many of the cases. However, a gradual decrease in the doses of antipsychotic drugs was initiated as the symptoms became stabilized. Moreover, in addition to the electroencephalographic recordings, measurements of plasma prolactin, noradrenaline, adrenaline, 17KS and 17OHCS in the urine and blood were made whenever possible; furthermore, LH-RH and TRH tests were made periodically, and the measurements of LH, FSH and TSH were also made.

Therapy with acetazolamide was attempted on 30 (27 females) cases with atypical psychosis and related diseases; they were classified into the following four categories on the basis of their clinical symptoms, courses and physiological and biochemical characteristics.

Type I: The first onset occurred at the puberal period of the female and, thereafter, psychosis-like symptoms such as acute con-

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fusion repeatedly and frequently appeared at the period corresponding the menstrual cycle. . . . 6 (6 females) cases (average age, 16.3) (This type will be abbreviated to puberal periodic psychosis in the following description).<sup>2 4</sup>

Type II: a) During the repetition of the cycle considered to be manic-depressive states, an acute hallucinatory-paranoid state, or dreamy and confused states began to appear repeatedly from about the presenile ages; these were incurable cases. . . . 7 (6 females) cases (average age, 51.0) (These cases will be called presenile atypical psychosis). b) A morbid episode occurred suddenly after adolescence, and a manic-depressive state, hallucinatory-paranoid state and delusion, dreamy and confusional states appeared repeatedly. . . . 8 (7 females) cases (average age, 25.5) (These will be described as atypical psychosis).<sup>3 6</sup>

Type III: A short-term manic-depressive phase appeared repeatedly and frequently for several years, which was accompanied by transient stuporous conditions and alteration of consciousness; these cases were known to be difficult to cure. . . . 2 (2 females) cases (average age, 59.0) (This type will be called atypical manic-depressive psychosis in the following).

Type IV: These cases were schizophrenia, but a recurrent type, and accompanied by a disturbance of feelings such as manic-depressive states and electroencephalographic abnormalities during the process. . . . 7 (6 females) cases (average age, 25.7) (This type will be abbreviated to atypical schizophrenia).<sup>8</sup>

## CASE REPORTS

### *Type I: A 14-year-old female*

(Previous History) Mental and physical development was normal and she had not suffered from any particular disease. She was an only child and was overly protected. In character, she showed a tendency of being

honest, punctilious, perfectionist and persistent; she was sensitive and timid outside but was remarkably dependent and selfish at home. Her grades were excellent through primary and junior high schools, and there was no problem in her personal relations.

(Present History) She experienced her first menstruation when she was 13 years and 9 months old; she began to loose her spirits and became absent-minded about one month after the first menstruation. During this period, a prolongation of sleeping time, reduced appetite and constipation were observed, and she subjectively complained of a dull and heavy head, inability to think, a reduced will to work and dreamy feelings. Thereafter, the above described symptoms disappeared at the beginning of her menstruation and a slightly manic state lasted for several days, which was followed by the recovery to a normal state. However, 2-3 weeks later, the above described conditions appeared again. Since then, this cycle appeared repeatedly; the length of the whole cycle was about one month. Electroencephalographic examinations were made, but no abnormalities were found. No change developed by the administration of antidepressants and tranquilizers. However, the administration of acetazolamide 500 mg without concomitant drugs produced the disappearance of the symptoms and the prophylactic effect was also attained through this treatment.

### *Type II-a: A 45-year-old housewife*

(Life History) When the patient was one year old, her mother disappeared. Thereafter, she was brought up by her paternal grandparents. After graduating from a girls' high school with good marks, she worked as an office girl. She got married when she was 28 years old. There no problems in bringing up her children.

Character: By nature, she was honest, punctilious, earnest in work and had a keen sense of responsibility. In addition, she was extroversive and cheerful.

(Present History) At about 22-23 years

old, hyperlogia and restlessness appeared without a precipitating cause which, however, healed spontaneously within several days. After marriage, she gave birth to her first daughter. Sleeplessness followed for 2-3 days immediately after the delivery; hyperlogia and hyperkinesia appeared, but they also healed spontaneously. At 38, she engaged in staff-work for the PTA and church. Triggered by the worries in arranging marriages, etc., she began to complain of sleeplessness, taciturnity and general fatigue in November of the same year. After these symptoms continued for a week, hyperlogia, loud singing, exaggerations and hyperkinetic poriomania appeared. Because of her condition, she was admitted to a hospital where she received medical care for about a month that produced a remission. At 39, after returning to the same work, she complained of sleeplessness, became taciturn and suffered from general fatigue; one week later, hyperlogia and restlessness appeared suddenly, and she prayed to God saying "My disease will heal with the help of Christ." However, her condition improved and a remission set in about four months. At 43, sleeplessness and taciturnity reappeared; monologia and delusion of self-accusation lasted for four days. Moreover, a stuporous condition appeared, which she was able to temporarily recover partially by the use of antidepressants. However, delusion of self-accusation became severe from which she subsequently fell into a stuporous condition. The symptoms changed within a day; the stuporous condition lasted from early morning to noon, and ecstasy, euphoric or dreamy state appeared with accompanying logoclonia-like speech in the afternoon. The morbid phase lasted considerably longer compared to that at the time of the first episode. Antimaniacal and antipsychotic drugs showed no effect. After the combined therapy with acetazolamide (benzanilamide), the symptoms gradually disappeared. The present agent also had a prophylactic effect on the appearance of the morbid phase.

(Laboratory Examination) A 6 Hz positive spike was observed after the remission. The urine levels of both noradrenaline and adrenaline were high.

*Type II-b: A 21-year-old female*

Slight mental retardation was observed by nature. After graduating from junior high school, she started working for a cotton spinning company and was appraised to be a hard worker. When she was 20, without a precipitating cause, hyperlogia, wastefulness and apastia appeared, and so the patient began to receive medical therapy. Thereafter, she was able to lead an ordinary social life, although her condition was still unstable, which was reflected by the mistakes in her work, etc. At 21, she suddenly visited her fiancé and did not return home. The parents went to fetch her, but she refused to go and became offensive. She complained of hot feelings in the body and sleeplessness. Moreover, she cried loudly saying "I became a star when I woke up from a dream. I dreamt that I became a singer. Japan will roll back the tide," etc., and then threw things around. Personal misidentification, erotic and indecent behaviors were clearly observed. This condition lasted for three weeks, but the clinical course was satisfactory during the therapy; there was no change in her personality. No recurrence was observed after the administration of acetazolamide. After the remission, she did not remember well the events that took place during the episode and said that it was like a dream. In electroencephalographic examinations, a slight slow wave was observed during the morbid phase and slow and spike waves after the remission. This was in accordance with the electroencephalographic features of atypical psychosis pointed out by Kimura.<sup>15</sup> Since carbamazepine 600 mg, chlorpromazine 150 mg and haloperidol 4.5 mg did not produce the suppression of the symptoms, carbamazepine was substituted by acetazolamide 1,000 mg; the symptoms improved after this substitution.

*Type III: A 64-year-old female*

(Present History) Punctilious and earnest in work by nature; thus, the patient is of an immodithymic character. At 53 years old, the patient suffered from manic-depressive psychosis without a precipitating cause, which was cured within a short period of time. Thereafter, at 56, she reverted to the same condition. When she was 61, she became depressive triggered by the sudden death of her son after which manic and depressive states appeared frequently and repeatedly. Under the depressive condition, delusions of self-accusation and poverty were most noticeable, and under the manic condition, she became excited and aggressive. At the time of the depressive condition, antidepressants were given; however, since a severe retention of the urine was observed, 500 mg of acetazolamide was administered, which produced an almost complete disappearance of the depressive and manic states. This medication also showed the prophylactic effect against the appearance of a morbid phase.

*Type IV: A 26-year-old male*

(Present History) Significant schizothymia shown by taciturnity, sensitiveness and earnestness, etc. At 23 years old, after graduating from university, he was given an injection by a certain physician because of the complaint of a nasal disorder immediately after getting a job. He retired from the job saying that he had a headache because he contracted a strange disease after the injection by the physician. After his retirement, he returned to his home in the Kyoto-Osaka area. However, at the same time, he suffered from a severe and significant auditory hallucination, delusion of persecution and syphilophobia and complained of a severe headache; soon after, he fell in a confusional and stuporous condition. For two years thereafter, the above described condition repeatedly appeared twice. With the medication of 200 mg carbamazepine and

antipsychotic drugs, he made a partial recovery from the symptom, but a recurrence occurred later. Thus, the medication was changed to 500 mg of acetazolamide, which partially improved the psychotic symptoms.

(Electroencephalography) A 6 Hz spike and wave complex.

(CT Scan) Slight temporal atrophy was observed.

## RESULTS

### 1. Therapeutic Effects of Acetazolamide on Patients of Each Morbid Type (Table 1)

Among the total 30 cases, acetazolamide was markedly effective in 23.3%, effective in 16.7%, slightly effective in 33.3% and ineffective in 26.7%; thus, some extent of the therapeutic effects was observed in 73.3%.

With respect to each morbid type, the therapeutic effect was obtained in 5 out of the 6 cases of puberal periodic psychosis. Among the 15 cases of presenile atypical psychosis and atypical psychosis, the number of cases in which acetazolamide was markedly effective or effective was 7 (46.7%). Thus, the high therapeutic effects of acetazolamide were observed in these two groups. Among the 7 cases of atypical schizophrenia, 4 cases showed a reduction of the symptoms after the administration of acetazolamide.

### 2. On the Relation between Psychopathological Findings and Therapeutic Effects of Acetazolamide (Table 2)

Among the subjects 23 cases showed the symptoms indicating an acute disorganization of mental function, i.e., a dreamy state with accompanying alteration of consciousness (6 cases), an acute excitatory or stuporous condition (6 cases), and acute confusional conditions considered to be accompanied by the disturbance of consciousness (6 cases); in 60% of these cases the antipsychotic effects of acetazolamide were observed.

Table 1: Atypical Psychosis and Therapeutic Effect of Acetazolamide

	No. of Subjects	Average Age (year)	Therapeutic Effect			
			Markedly effective	Effective	Slightly effective	Ineffective
Group I:						
Puberal periodic psychosis	6 ( 6)	16.3	3 (3)	1 (1)	1 (1)	1 (1)
Group II:						
a) Presenile atypical psychosis	7 ( 6)	51.0	1 (1)	3 (2)	2 (2)	1 (1)
b) Atypical psychosis	8 ( 7)	25.5	2 (1)	1 (1)	2 (2)	3 (3)
Group III:						
Atypical manic-depressive psychosis	2 ( 2)	59.0	1 (1)		1 (1)	
Group IV:						
Atypical schizophrenia	7 ( 6)	25.7			4 (3)	3 (3)
Total	30 (27)		7 (6) (23.3%)	5 (4) (16.7%)	10 (9) (33.3%)	8 (8) (26.7%)

Number in ( ) is the number of female cases.

Table 2: Clinical State and the Effect of Acetazolamide

Clinical State	Therapeutic Effect (+)	Therapeutic Effect (-)
Dreamy state	6	1
Acute excitement and stupor	6	3
Acute confusional state	6	1
Manic state	2	1
Acute hallucinatory-paranoid state	1	1
Vegetative symptoms	1	1
Total	22	8

Acetazolamide had a little effect on the conditions of hallucination and delusion.

### 3. On the Aggravation of Mental Symptoms Accompanied by the Sexual Cycle and the Effects of Acetazolamide

In all of the cases, 8 female patients showed a clear aggravation of the mental symptoms accompanied by the sexual cycle. Among these 8 cases, some extent of the therapeutic effect was obtained by the administration of acetazolamide in 5 cases (62.5%); marked effects were obtained in 3 cases. In contrast, 12 female cases did not

show the aggravation of mental symptoms related to the sexual cycle although they showed regular sexual cycles. Among these cases, acetazolamide showed some therapeutic effects in 9 cases (75%), when including slightly effective cases. Thus, there was no significant difference between the therapeutic effects of acetazolamide on the group showing the sexual cycle-related aggravation of the mental symptoms and on the group without showing the sexual cycle-related changes. However, acetazolamide was either markedly effective or effective in 50% of the cases showing the sexual cycle-related aggravation of the mental symptoms, while it was 25% in the cases without showing the sexual cycle-related changes. Therefore, it was found that acetazolamide tended to show higher therapeutic effects in the former group.

### 4. On the Cases Accompanied by Abnormalities in Electroencephalography and the Effects of Acetazolamide

Among all of the subjects, 14 cases showed abnormalities in electroencephalography (46.7%), and 16 cases did not show such abnormalities (53.3%). The electroencephalographic abnormalities observed

were: 1) a slow wave at the morbid phase in 5 cases, 2) a tendency of a slightly slow wave at the morbid phase followed by the augmented slow wave and spike accompanied by the gradual healing of the morbid phase in 2 cases, and 3) a 6 Hz positive spike or spike and slow wave complex in 7 cases. In the group with accompanying electroencephalographic abnormalities, some extent of the therapeutic effects was obtained after the administration of acetazolamide in 11 cases (79.6%). In contrast, in the group without showing the electroencephalographic abnormalities, some extent of the therapeutic effects of acetazolamide was observed in 11 cases (68.7%). Thus, acetazolamide showed slightly higher therapeutic effects in the group with the electroencephalographic abnormalities. However, there was no statistically significant difference between the effects in both groups.

#### 5. Prophylactic Effects of Acetazolamide against the Appearance of the Morbid Phase in Atypical Psychosis (Table 3)

To determine the prophylactic effects of acetazolamide, it is necessary to observe the process for a long period of time. Therefore, the results obtained in the present study are not considered to be sufficient, partly because the results included the cases now undergoing therapeutic examinations. However, 9 cases did not show the periodicity over two years after the administration of

acetazolamide. Among these cases, the morbid phase did not appear after the administration of acetazolamide in 4 out of the 6 cases of group I. Among the 15 cases of groups II-a) and b) inhibition of the periodicity was observed in 4 cases. The number of cases was as few as 2 in group III. However, in these 2 cases, one in which the manic and depressive phase had been observed frequently did not show the morbid phase after the administration of acetazolamide.

Recently, lithium carbonate or carbamazepine had often been administered in order to prevent the appearance of the morbid phase of atypical psychosis. The present authors also tried to administer the above drugs to the present subjects to eliminate the morbid phase (Table 4). As a result, 5 cases showed an aggravation of the symptoms in spite of the administration of lithium carbonate. Moreover, 3 cases showed an improvement after changing the drug to acetazolamide. Among the cases in which the prophylactic effects of carbamazepine were examined, 8 cases showed a symptomatic aggravation during the course of its administration; among these 8 cases, the prophylactic effects against the appearance of the morbid phase were observed in 7 cases after the administration of acetazolamide. In other words, among the total 13 cases in which either lithium carbonate or carbamazepine were unable to produce the prophylactic effects, the administration of acetazolamide produced the prophylactic effects

Table 3: Prophylactic Effect of Acetazolamide against Atypical Psychosis

	No. of Subjects	Prophylactic Effect (%)
Group I	6	4 (66.7)
Group II		
a)	7	2 (28.6)
b)	8	2 (25.0)
Group III	2	1
Group IV	7	0
Total	30	9 (30.0)

Table 4: Therapeutic Effect of Acetazolamide

Cases to which Therapeutic Drugs to Protect Periodicity Were Ineffective	No. of Subjects	Effect of Acetazolamide (%)
Lithium carbonate	5	3
Carbamazepine	8	7
Total	13	10 (76.9)

against the appearance of the morbid phase in 10 cases (76.9%).

#### 6. On the Physiological and Biochemical Changes after the Administration of Acetazolamide

After the administration of acetazolamide, no change was observed in the general examinations of the serum electrolytes, blood and urine.

A decrease in urinary noradrenaline and a decreasing tendency in plasma noradrenaline were observed in 4 cases after the administration of acetazolamide. (Care should be taken when determining the urinary noradrenaline and adrenaline, because these concentrations may be influenced by alkalosis, possibly produced by the administration of acetazolamide.)

In addition, one method for predicting the antipsychotic effects is to measure the increase in the plasma prolactin level due to the antidopaminergic effect after the administration of acetazolamide. In the present study, even when an antipsychotic drug was kept in constant use, the plasma prolactin level tended to increase in 3 cases after the administration of acetazolamide. Moreover, since disorders are presumed to be present in the hypothalamo-hypophyseal system in atypical psychosis, LH-RH and TRH were loaded intravenously during the morbid and remission phases. In the present study, LH-RH or TRH were loaded in 9 cases, and LH, FSH, TSH,  $T_3$  and  $T_4$  were measured after the loading. However, it was unable to obtain sufficient results, suggesting the presence of disorders in the hypothalamo-hypophyseal system.

### DISCUSSION

#### 1. On the Therapeutic Effects of Acetazolamide on Atypical Psychosis

From the results of the present therapeutic study, acetazolamide was found to be either markedly effective or effective on 12

cases (40%) of puberal periodic psychosis, presenile atypical psychosis, atypical psychosis, in the narrow sense, and atypical manic-depressive psychosis; when including the cases in which the present agent was slightly effective, it was effective in 73.3% of the total cases. Acetazolamide is considered to have antipsychotic effects especially on puberal periodic psychosis, atypical psychosis, in the narrow sense, presenile atypical psychosis and atypical manic-depressive psychosis. With respect to the individual symptoms, the present agent was effective especially on a dreamy state, acutely excitatory or stuporous states and acute confused state.

In the therapy of atypical psychosis, it is important to exert the prophylactic effect against the appearance of a morbid phase; in the present study, acetazolamide produced the inhibitory effects on the periodicity in 9 cases (30%). This effect was especially marked on puberal periodic psychosis. As described later, lithium carbonate<sup>20</sup> and carbamazepine were used generally for preventing the periodicity in atypical psychosis. However, in the present study, it was noted that both agents did not show the inhibitory effect, but acetazolamide did show such effect in some of the cases.

Summarizing the previous studies on the therapy of atypical psychosis, the following agents have been used: antipsychotic agents, lithium carbonate, carbamazepine, progesterone, estrogen, thyroid and anterior pituitary hormones and ECT.

In the therapy with antipsychotic drugs, they are used in an attempt to obtain the tranquilizing effect. However, in the cases of psychotic symptoms of atypical psychosis, it is difficult in many cases to expect these drugs to exert sharp antipsychotic effects.

With respect to the hormone therapy with progesterone, etc., they were reported to be effective especially on puberal periodic psychosis and postpartum psychosis. From the consideration that these psychoses may be caused by the excess estrogen derived from



the fragility of the hypothalamo-hypophyseal system, this therapy is attempting the homeostatic control by giving progesterone. Hatotani<sup>5</sup> suspected the abnormalities of steroid metabolism in the liver on the basis of the finding that aldosterone decreases relatively, and so he administered thyroid hormones to bring under control the disorders in the hypothalamo-hepatic homeostasis. Hatotani<sup>5</sup> reported that the therapeutic effects were obtained in 76% of atypical psychosis by using anterior pituitary hormone, female sex hormone and thyroid hormone, etc. Moreover, recently, on the basis of the neuroendocrinological studies, Yui *et al.*<sup>22</sup> attempted therapy on puberal periodic psychosis with progesterone. Therefore, in the present therapeutic study, neuroendocrinological examinations were conducted by loading LH-RH (100  $\mu$ g) during the morbid and remission phases. As a result, abnormality was found only in one out of 6 cases. Moreover, sufficient studies have not yet been carried out on the prophylactic effect of hormone therapy against the appearance of the morbid phase, and the application of hormone therapy has not yet been established.

Among the 30 cases subjected to the present study, some cases showed the electroencephalographic changes such as a seesaw phenomenon described by Kimura,<sup>15</sup> 6 Hz positive spike, and slow wave of the basic rhythm, etc. On the basis of the above findings, and also considering the fact that some antipsychotic drugs produce a decrease in the threshold of convulsions, it is reasonable that therapy with antiepileptic drugs, especially with carbamazepine, to be taken into consideration. Okuma *et al.*<sup>16, 17</sup> reported that 70% therapeutic effects were obtained with carbamazepine on manic-depressive psychosis, and that it possessed the inhibitory effect on the periodicity.

Recently, Inose *et al.*<sup>7</sup> described that carbamazepine had been effective on manic-depressive psychosis accompanied by electroencephalographic abnormalities (which seemed to be considered as atypical psy-

chosis). In addition, Kameyama *et al.*<sup>18</sup> reported recently that carbamazepine had been effective on cases exhibiting the schizophrenia-like symptoms accompanied by electroencephalographic abnormalities. The present authors attempted therapy with carbamazepine in 8 cases out of the total 30 cases subjected to the present study. However, no therapeutic effects were obtained in all of these cases. In many of the cases during the present experiment, the administration of carbamazepine was discontinued because its application unexpectedly produced a reduction of inhibition, or the therapy was changed to acetazolamide therapy because carbamazepine did not show the prophylactic effects.

Acetazolamide has been used clinically as an antiepileptic agent. As its pharmacological mode of action, it has been proposed that it can control the acid-base balance as a mechanism of carbon dioxide disposition, can reduce the membrane permeability by increasing the extracellular and intracellular Na ion ratio and that it can also produce the anticonvulsive action in the presence of brain amines, etc.<sup>11, 18, 21</sup>

With respect to its anti-manic activity, Inui<sup>11</sup> compared the pharmacological actions between lithium carbonate and acetazolamide, and reported that both agents had a similarity in nature. In other words, lithium carbonate did not affect the Na-pump, but Li ion disturbed the electrolyte balance through the cell membrane by accumulating intracellularly, thus producing the inhibition of the membrane permeability to Na ion. In addition, lithium carbonate has the anticonvulsive action under the condition of L-Dopa load and in the presence of brain amines. Thus, the author proposed that both agents had a similarity in their action. Electroencephalographic abnormalities were observed in 14 out of the 30 present cases of atypical psychosis. From this result, it can be considered that acetazolamide showed its effects as an anticonvulsive agent in the present cases.

In the biochemical studies on atypical

psychosis, it was initially noted that, on the basis of the high estrogen level, puberal periodic psychosis was caused by the accumulation of Na and water. Moreover, Tanimukai<sup>21</sup> hypothesized that manic-depressive psychosis was caused by "abnormalities in the brain electrolyte metabolism," or "abnormalities in the brain amines." He proposed that there were disturbances of a brain electrolyte, Na ion, in the patients showing strong anxiety and irritation. It was also described that, in manic-depressive psychosis, Na, Ca, Na/K were reduced in the cerebrospinal fluid in the case of a manic state, and that an increase in Na/K and a decrease in K were observed in the cerebrospinal fluid in the case of schizophrenia.<sup>1</sup> From these points of view, it is possible that the effect of acetazolamide on the electrolyte balance may produce advantageous effects in the therapy.

Among the cases of atypical psychosis examined in the present therapeutic study, some cases showed the high plasma levels of noradrenaline and adrenaline during the morbid phase, which were reduced after the administration of acetazolamide. And, in contrast, acetazolamide was ineffective in the cases whose noradrenaline and adrenaline plasma levels were abnormally low. These findings may suggest the relationship between atypical psychosis and brain amines. Izumi *et al.*<sup>12</sup> attempted the reserpine therapy on atypical psychosis and reported that it was effective. However, reserpine is said to rather decrease the brain amines.

Schnell *et al.*<sup>10</sup> reported on the doubling of brain concentration of chlorpromazine by the administration of acetazolamide. In the present study, the plasma prolactin levels were examined in some cases with keeping the antipsychotic drugs constant; among these cases, an increase in plasma prolactin was observed in 3 cases after the administration of acetazolamide. With respect to this result, it can be considered that it was due to the potentiation of the anti-DA action of antipsychotic agents. However, the fact that

there were some cases of puberal periodic psychosis which have been cured by the exclusive administration of acetazolamide may indicate the possibility that acetazolamide *per se* possesses antidopaminergic effects.

Since the periodic cycle repeatedly appears in the case of atypical psychosis, it is required to be observed for a long period of time. Of great interest was the finding that acetazolamide was able to exert the prophylactic effect against the appearance of the morbid phase in some cases in which lithium carbonate did not produce the prophylactic effect. In the cases of manic-depressive psychosis of the rapid cycle, it is generally said that the inhibition of the periodicity is difficult to be produced with lithium carbonate. Therefore, it should be important to know the therapeutic effects of acetazolamide on these cases. However, in these cases, therapy is usually discontinued when there is a remission; therefore, it is not always possible in many of the cases to perceive the prophylactic effect against the appearance of the morbid phase. In this respect, sufficient guidance should be needed in administering therapy.

In addition, with respect to the optimal dose of acetazolamide, we consider that 500 mg or 1,000 mg are necessary from our experience. However, it is necessary to make further examinations in the future with respect to the relationship between the plasma concentration of acetazolamide and clinical effects, and to the mutual interaction between acetazolamide and antipsychotic drugs.

In conclusion, we would like to mention that sleepiness and a feeling of numbness of the fingers were the source of complaints as the side effects during the course of the acetazolamide therapy. However, no influence was observed on the serum electrolytes, cardiac function, liver function test and renal function. Thus, it is considered that acetazolamide is a drug with a high degree of safety and that its use is highly recommended as compared to lithium carbonate.

## SUMMARY

Studies on therapy with acetazolamide were conducted in 30 cases of atypical psychosis (puberal periodic psychosis, 6 cases; presenile atypical psychosis, 7 cases; atypical psychosis, 8 cases; atypical manic-depressive psychosis, 2 cases; atypical schizophrenia, 7 cases). Acetazolamide was administered at doses of 500 mg–1,000 mg as the daily doses. Although acetazolamide was exclusively administered in principle, antipsychotic drugs were concomitantly administered in the cases with severe psychotic symptoms; the doses of antipsychotic drugs were reduced with the symptomatic improvements.

1) Acetazolamide was either markedly effective or effective in 40.0% and slightly effective in 33.3%. Its therapeutic potency was specially high on puberal periodic psychosis, presenile atypical psychosis and atypical psychosis.

2) With respect to the individual symptoms, a 60.0% therapeutic effect was achieved on a dreamy state, acute excitatory, stuporous and acutely confused states.

3) Regarding the cases whose psychotic symptoms aggravated in connection with the sexual cycle (8 cases) and those accompanied by the electroencephalographic abnormalities (14 cases), the therapeutic effects were obtained in 62.5% and 79.6%, respectively.

4) The prophylactic effect against the appearance of the morbid phase was observed in 9 cases after the administration of acetazolamide; especially, the prophylactic effect was highly noticeable in the case of puberal periodic psychosis. Cases in which both carbamazepine and lithium carbonate were ineffective but acetazolamide was effective were 3 out of 5 cases and 7 out of 8 cases, respectively.

From these results, it was conclusively considered that acetazolamide produced the antipsychotic and prophylactic effects on atypical psychosis.

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