Gamma-Hydroxybutyrate Treatment of Schizophrenia: A Pilot Study

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Summary
Gamma-hydroxybutyrate (GHB) was administered to seven chronic schizophrenic patients in the first double-blind, placebo-replacement trial of this compound. No significant drug effect in this group was obtained. Two patients became non-psychotic during the drug trial, three got worse and two patients did not respond. The two patients who responded with improvement were augmenters, as measured by average evoked potential (EP), had low platelet MAO activity and high cerebrospinal fluid (CSF) homovanillic acid (HVA). A number of patients developed akathisia and dystonia during the trial, especially after receiving probe-nedic for lumbar puncture. Further study is warranted, possibly in a selected patient group.

Gamma-Hydroxy-Buttersäure in der Behandlung der Schizophrenie — Bericht über 7 Patienten

Bei der Betrachtung der Ergebnisse der 7 Patienten war ein medikamentöser Effekt auf die schizophren Symptomatik nicht erkennbar (Tabelle 2). Bei der Einzelfallbetrachtung ergab sich, daß 2 Patienten symptomfrei wurden, 2 Patienten zeigten keine Reaktion und 3 eine Symptomverschlechterung.

Eine explorative Datenanalyse erbrachte für die 2 Patienten, die symptomfrei wurden, einige interessante Ergebnisse bezüglich der Konzentration der Homovanillinsäure in der Zerebrospinalflüssigkeit und der Monoaminoxidaseaktivität in den Thrombozyten (Abb. 1): Bei den beiden Respondern scheint die Homovanillinsäurekonzentration höher, die Monoaminoxidaseaktivität niedriger und die Reaktion auf die visuelle Reizung stärker zu sein als bei den Non-respondern.

Es wird die These aufgestellt, daß γ-Hydroxy-Buttersäure unabängig oder über GABA-erge Mechanismen die Aktivität dopaminerge Neurone vermindert und so bei bestimmten biochemischen und neurophysiologischen Voraussetzungen eine Wirkung auf schizophren Symptomatik haben kann.

Introduction
Gamma-hydroxybutyrate (GHB) is an endogenous compound found in the mammalian (Roth and Giarmann, 1970) and human (Doherty et al., 1976) brains. Rubin and Giarmann (1947) noted that gamma-butyrolactone (GBL), a GHB congener, suppressed muscle activity in mice. Later, GBL was found to be metabolized in the liver to GHB, a central nervous system (CNS) active compound (Rubin and Giarmann, 1947; Roth and Giarmann, 1966; Fishbein and Bessman, 1966; Roth et al., 1967). Laborit et al. (1960, 1961) were the first to note GHB's anesthetic properties which led to its clinical use in Europe. Since that time there have been numerous investigations into the mechanism of action of GHB. Some early investigations have suggested that GHB may act through the gamma-aminobutyric acid (GABA) system (Roth and Nowycky, 1977; Stock et al., 1973), while others (Olpe et al., 1977) have reported that GHB's effects are independent of GABA mechanisms. GHB's possible relationship to sleep (Marmelak et al., 1977) and Huntington's Chorea (Ando et al., 1979) continue to be actively investigated. Snead (1976) reviewed the correlations between blood and CSF levels and seizure activity on EEG in cats. Similar EEG patterns were noted in rats (Godschalk et al., 1977).

Of great interest in the relationship of GHB and psychosis are the experiments concerning GHB's effect on the central neurotransmitter systems. GHB inhibits the firing-rate of dopaminergic neurons (Nowycky and Roth, 1979; Olpe and Koel, 1979; Roth et al., 1973; Walters et al., 1972) in the CNS. This inhibition of dopamine-firing has been found to produce biochemical effects similar to those of electrolytic atoxyn (Andén and Stock, 1973; Walters et al., 1973). GHB has been found to increase brain dopamine (DA) (intracellular), presumably due to its ability to block impulse flow and DA release but has no effect on steady state levels of norepinephrine (NE) (Gessa et al., 1966; Spano et al., 1971; Aghajanian and Roth, 1970; Roth and Surh, 1970). Comprehensive reviews on the pharmacological and biochemical properties of GHB have been published recently (Walters and Roth, 1977; Snead, 1977).

Having found differential effects of GHB on dopaminergic tracts in the limbic system, compared to striatal tracts (Lundahl and Fuxe, 1975; Fuxe et al., 1977), some investigators then suggested that the drug should be tried in schizophrenic patients (Walters and Roth, 1977; Fuxe et al., 1977, van Kammen, 1977). According to the DA hypothesis of schizophrenia, drugs that would decrease DA activity, particularly in the mesolimbic DA tract, could have antipsychotic effects (van Kammen, 1979; Melzer and Stahl, 1976; Stevens, 1975). GHB has been tried in some neurologic disorders in which DA presumably plays a role, such as Huntington's Chorea (McGeer et al., 1977), Parkinson's Disease and the muscle cramps of cerebral palsy (van Woer, 1975).

Some studies have noted that GHB is helpful in decreasing...
anxiety and agitation in some subjects (DuCovedic et al., 1964; Dannon-Boileau et al., 1962). Tanaka et al. (1966) administered GHB or GBL nonblind to 248 psychiatric patients, 48 of whom suffered from chronic schizophrenia. Most improvement was seen in hebephrenics (5/7) and catatonics (60%) [number of patients not given]. Only two of six schizophrenic patients with hallucinations and delusions improved.

The present study was undertaken to evaluate, under double-blind, placebo-controlled conditions, the therapeutic claims for GHB on the symptoms of seven schizophrenic patients and, also, to further examine the DA hypothesis of schizophrenia. Similarly, we evaluated high-dose diazepam in a small group of schizophrenic patients (Jimerson et al., submitted for publication).

Methods
 Seven schizophrenic patients (3 males and 4 females) who were diagnosed with the RDC criteria of Spitzer et al. (1978) and with at least four symptoms (range 4–10; means 7) of the International Pilot Study of Schizophrenia (IPSS) (Carpenter et al., 1973) participated in the study (Table 1). Patients gave written informed consent and, in most cases, so did a member of their families. All patients were physically healthy and adhered to a controlled monoamine diet.

GHB administration was preceded by at least a 10-day placebo period and followed by a placebo period of 10 days. Neither patients nor staff were aware of when the trial started as there was no change in the number or characteristics of the capsules. The beginning dose was 2 grams/day in five equally divided doses and was increased approximately every four days until a maximum dose of 8–16 grams was reached. The drug trial lasted an average of 23 days (range 10–29 days). Behavior and movement disorders were assessed daily. Global psychosis ratings (modified Bunney-Hamburg Scale) (Bunney and Hamburg, 1963) were obtained daily by the nursing staff and weekly by the psychiatrists who were blind to the medication administration. Furthermore, the psychiatrists completed the Brief Psychiatric Rating Scale (BPRS) to evaluate each patient weekly. Both groups entered their observations into the medical charts. Weekly, clinical laboratory studies were performed (CBC, liver function, renal function, electrolytes and thyroid function). Blood levels of GHB were drawn at various doses during the trial one hour after the last dose in the morning. GHB levels were measured by the spectrophotometric method, with a modification of the Hestrin assay by one of us (R.H.R.) (Hestrin, 1948; Guidotti and Balloti, 1970).

Fig. 1 Spinal fluid HVA, platelet MAO and AER data obtained during placebo prior to GHB medication trial. Left: CSF-HVA. Mean CSF-HVA for controls analyzed by mass spectrophotometry is 28.2 ± 3.89 (N = 16) (Post et al., 1979). Center: Platelet MAO activity: MAO is expressed as a corrected value for gender (see Methods) thus the mean value in normals is zero. Right: EP amplitude/intensity slope. The mean value in 95 normals was 0.69: 90th percentile 1.98 and 10 percentile –0.60.

Fig. 2 Individual double-blind psychosis ratings by the nursing staff. The data are presented as 3-day running means. Each patient had been drug-free at least 2 weeks prior to each LP before the beginning of GHB treatment. Shaded areas indicate time of actual GHB treatment. GHB was administered in divided doses five times each day.
Baseline lumbar punctures (LP's) were obtained on all patients. Probencid LP's were obtained on four patients before and during GHB treatment. Probencid was administered in four divided doses (100 mg/kg) over an 18-hour period prior to the LP. LP's were performed with patients in the lateral decubitus position between 8:30 and 9:00 a.m. following nine hours of bed rest (van Kammen and Sternberg, 1980). 3-Methoxy-4-hydroxyphenylglycol (MHPG) and homovanillic acid (HVA) were measured with mass spectophotometry (van Kammen and Sternberg, 1980). Following the probencid LP, which took place between 2:30 and 3:00 p.m., patients who experienced nausea or vomiting as a side effect of probencid were given trimethobenzamine. During a drug-free period prior to the LP, platelet MAO activity was measured using benzylamine tagged with $^{14}$C as substrate (Murphy et al., 1976). The MAO activity value used in this study was corrected for gender differences by subtracting the mean MAO for each sex from two large comparison groups to allow combining of male and female subjects (males: 11.04 ± 2.9, N = 348 and females: 13.29 ± 2.9, N = 332) (Murphy et al., 1976).

Average evoked potentials (EPs) to four intensities of light were recorded as described elsewhere (Buchsbaum, 1978). Each patient in this drug trial underwent EP testing before receiving the drug. The results are reported as the amplitude/intensity slope for Vertex P100 component which has been postulated to separate a group of „augmenters” (stimulus intensity augmenters) from „reducers” (stimulus intensity reducers) (Buchsbaum, 1976).

### Table 1

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Drug-Free</th>
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<th>Change</th>
<th>Withdrawal</th>
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<td>6</td>
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<td>7</td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>C.S.Un.</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Mean</td>
<td>25</td>
<td>2.5</td>
<td>7</td>
<td>2.5 yrs.</td>
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### Results

Two patients improved, three did not change and two worsened (see Table 2). The median global psychosis rating for the seven patients was 5.8 (15-point scale) in the drug-free baseline period, 7.1 during maximum drug dose and 6.0 in the week after GHB. The nurses' global psychosis ratings agree with the ratings by the psychiatrists using the BPRS items indicative of psychosis.

In an attempt to find discriminating characteristics among the two responders and the other patients, CSF HVA, platelet MAO activity and EP, were examined in relationship to change in psychosis. As can be seen in Fig. 1, the responders had a higher mean HVA before the trial. Probencid LP's prior to and during GHB treatment (obtained in 4/7 patients) revealed a slight decrease on drug for the mean HVA of the group. However, the two responders showed HVA values moving in opposite directions during GHB treatment. CSF MHPG was not changed significantly by GHB either (not shown). The platelet MAO values (corrected for sex) are displayed in Fig. 1 and show the mean value for the responders to be lower than for the nonresponders. The data in Fig. 1 show that the two responders were marked augmenters on the EP measure prior to the GHB trial. The correlation between psychosis improvement and EP amplitude/intensity slope did not reach statistical significance (r = .66) but compared to the nonresponders, there was no overlap in this measure (Fisher's Exact Test, p < 0.05, 1-tailed).

Blood levels were not always obtained on highest doses but each responder or worserer had a blood level equal to or higher than the responders, indicating that nonresponse was probably not secondary to not taking the drug, inadequate absorption or increased metabolism.

Various movement disorders were noted during the GHB trial and included extrapyramidal effects (cases 1, 2, 3, 4, 6), akathisia (case 5), dyskinesia (cases 1 and 6) and leg muscle cramps (case 2). Strikingly, many of these movement disorders were noted following administration of probencid for the LP. The patient who suffered muscle cramps also had marked diuresis. Although GHB is administered as a salt and, therefore, the patient may lose potassium with the accompanying diuresis, neither this patient nor any other had abnormal potassium levels.

Figure 2 and the following case reports describe the response of the patients to GHB.

### Case No. 1: Initial Worsening Followed by Antipsychotic Response

Patient DR has a three-year history of psychosis characterized by auditory and visual hallucinations. She previously had been treated with haloperidol without much improvement. The patient had two siblings with psychosis, one of whom had been diagnosed as having schizophrenia. Previously, she had experienced thought insertion, thought blocking and multiple voices commenting on her behavior. As noted in the graph, the patient was moderately psychotic before her GHB trial. On the second and third days of taking the drug, the patient had an increase in hallucinations. She showed confusion and reported feeling sedated. Seven days after GHB was started the nursing staff noted that the patient was definitely improved, compared to before beginning GHB. By the 20th day of GHB treatment the patient was functioning well socially and psychotic symptomatology had disappeared. At this time she experienced four days of subtle oral-buccal-lingual dyskinesias, a symptom she had not shown previously.
Case No. 2: Partial Improvement with Remission Upon Withdrawal

Patient PD is a 34-year-old female with a one-year history of psychosis and depression that began simultaneously following a hysterectomy. Her first hospitalization took place after she attempted to strangle her daughter in response to her fear of being killed by her father. She had two siblings diagnosed as schizophrenic. When she began the GHB trial, she suffered from nonaffective auditory and visual hallucinations, flattened affect, depressed feelings and paranoid delusions. Prior to the drug trial, the patient had paranoid ideas about research and had visual hallucinations of fires in her room. On the second day of the drug trial she had fewer hallucinations and found them less troubling (4 mg GHB/day). After nine days of GHB she had no hallucinations but experienced leg cramps following a probenecid LP. Two days prior to the end of the trial the patient said she was not depressed and did not hear voices. She experienced some hallucinations two days after GHB was discontinued but had no psychotic or depressive symptoms thereafter.

Case No. 3: Minimal Change in Psychosis

The patient is a 24-year-old male who suffered symptoms of paranoid, disorganized thinking that at times made him incoherent with inappropriate affect for two years prior to admission. He was described as being a loner but had performed well until his senior year of college when he developed persecutory delusions concerning homosexuals. He had one prior hospitalization during which he was treated with thioridazine, without much effect. He had a paternal aunt with schizophrenia. On admission he showed thought disorder, auditory and visual hallucinations, delusions and thought insertion. Before the drug trial, the patient changed little with the exception of becoming more suspicious. After one week on GHB he appeared more withdrawn and autistic. During probenecid pretreatment for his LP he was noted to become even more autistic and to have marked increase in stereotypes and oral dyskinesias. The movement difficulties decreased after two days and were markedly better in two weeks. Clinically, the patient was somewhat better at the very end of his drug trial. When withdrawn from GHB, he worsened markedly, characterized by increased rituals and hallucinations.

Case No. 4: Slight Worsening in Psychosis

The patient is a 26-year-old female with a three-year history of psychosis characterized by a well-organized paranoid delusion that the Mafia was going to kill her, marked ideas of reference and mild thought disorder. Prior to being admitted to NIMH, she had two episodes of running away from home because of her fear of being killed by her father. She had two siblings with schizophrenia. On admission she exhibited thought disorder, poor insight, persecutory delusions and ideas of reference. Prior to her GHB trial the patient remained unchanged from her admission condition. On her first day of GHB she reported hearing voices in her head commenting on her sins. Two days later she heard the voices of the Mafia. Throughout her drug trial, she remained delusional and continued to feel depressed. Following probenecid LP the patient experienced muscle stiffness and bradykinesia. On the last two days of GHB, the patient began to include staff members into her hallucinations. Six days after the end of the drug trial the patient mentioned her delusions much less often and, for the first time, began to consider the possibility that her persecutory ideas might be delusions.

Case No. 5: Slight Worsening in Psychosis

The patient is a 23-year-old male who has been psychotic for seven years, characterized by thought blocking, delusions of being possessed by demons and immobilizing paranoia. Both his mother and maternal grandmother suffered from schizophrenia. Prior to the GHB trial, the patient had auditory hallucinations and frightening delusions that led to his keeping his back to the wall; however, he was able to participate in some milieu activities and individual therapy sessions. His illness had an undulating course with intensification of psychosis during the latter two-thirds of the study. He was noted to suffer from severe akathisia on a number of days throughout the trial (see Figure 2). This symptom disappeared in the placebo-replacement (postGHB) period.

Case No. 6: Minimal Change in Psychosis

This patient is a 23-year-old man who had the onset of psychosis at age 16. Three years before admission to our unit, he began receiving messages from television and acting on these messages. He was also experiencing auditory hallucinations, social withdrawal and thought disorder. The patient had been treated with fluphenazine without reduction of symptoms and had been steadily hospitalized. On admission he suffered from thought disorder, derealization and depersonalization. Four days prior to beginning the GHB drug trial, the patient was noted to be somewhat improved compared to admission. He had decreased ideas of reference and was more logical. On the first day of GHB his thinking appeared slowed, his talk was metaphorical and he had trouble relating to others. After three days of GHB, the patient was described as having marked hallucinations, experiencing thought insertion and racing thoughts. Eight days after GHB was discontinued, the patient was described as considerably improved: he was less withdrawn, less referential and was not hallucinating as much as during the drug trial.

Case No. 7: Worsening with GHB

The patient is a 31-year-old female who had an eight-year history of chronic schizophrenic psychosis. She had been able to work with only occasional hospitalizations. Two years prior to admission to our study she continuously became more psychotic with her main symptoms being auditory
hallucinations and delusions with religious content. Two days following the initiation of GHB, the patient became increasingly negativistic and psychotic. On the eighth day of the trial she was markedly psychotic. She showed pressure of speech, decreased sleep and was sexually provocative at which time she introduced herself to the other patients as the wife of her psychiatrist. This behavior resembled her response to a double-blind infusion of 20 mg of amphetamine performed earlier in another study (van Kammen et al., submitted for publication). She had one period of approximately four days during which her psychosis level returned to nearly pretrial levels but this trend abruptly ended by a switch back to the excited behavior (as seen during the last week of GHB treatment). Interestingly, five days after GHB was stopped, the patient remarked, "I'm feeling a lot better!" This was corroborated by the double-blind observations of the staff, who noted she appeared to be less psychotic.

Discussion

This is the first double-blind, placebo-replacement investigation of the effects of GHB on the symptoms of schizophrenia. Two of the seven patients in the study improved while they were taking the drug. The patients who improved received ratings in the nonpsychotic range. Both responders had been observed to have stable psychopathology for over two months, improved more than with previous treatments and remained nonpsychotic for some time following the drug trial. Although this may raise some questions about GHB's being the causal agent of the improvement, other treatments of schizophrenia, such as neuroleptics, are not followed by relapse immediately on withdrawal. However, several patients experienced exacerbation of their psychosis sometimes associated with increases in the dose of GHB.

Despite the small sample size of this study, the double-blind design in which the patient serves as his own control makes the response of the two patients who responded interesting, especially because of current formulations of the heterogeneity in the etiology of schizophrenia (Buchsbaum and Rieder, 1979).

GHB, whether it acts independently or through a GABAergic mechanism, decreases the firing-rate of dopaminergic neurons (Walters et al., 1972; Olpe and Koella, 1979; Roth et al., 1973; 1980). In addition, GHB appears to be active particularly in the mesolimbic DA tracts (Fuxe et al., 1977). It is conceivable that the responders were patients with a heightened dopaminergic tone. The nonresponders may have been a group in which a different mechanism led to their psychosis. High preGHB CSF HVA (an indicator of DA turnover) was associated with a decrease in psychosis. In addition, probenecid LP's were not helpful in determining how GHB interacted with DA in a clinically relevant way. HVA values increased in one responder but decreased in the other; the same was true for the two nonresponders who had probenecid LP's.

It is of interest that the two responders had both low MAO activity and an augmenting response on the EP. This combination has been predictive of risk for suicidal attempts in normal and psychiatric populations (Buchsbaum, 1976; Buchsbaum and Rieder, 1979) and as a predictor of risk for affective and other symptoms in volunteer populations (Haier et al., 1979).

To enhance GHB levels, probenecid could be administered simultaneously. As the authors have noted, a number of patients develop motor difficulties after taking probenecid while on GHB. The possibility exists that probenecid decreases the urinary excretion of GHB and also interferes with the transport out of the CSF. If this could be confirmed, a lower dose of GHB could be given with probenecid and a more stable blood level maintained.

The interaction of GHB with neuroleptics was not studied. This possibility has been suggested by other workers and, in light of the results of this study showing two responders to GHB alone, should be investigated.

Finally, in this study GHB seemed to be an antipsychotic agent in two patients who had not previously shown a satisfactory response to antipsychotic drugs. Further study is warranted: patients who are unresponsive to neuroleptics, have high CSF HVA levels and are augmenters on the EP with low platelet MAO activity may be potentially successful candidates.

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