Methione Effects on Chronic Schizophrenics

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Patients Treated With Monoamine Oxidase Inhibitors

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Introduction

IN 1952, Osmond and Smythies and Harley-Mason suggested the possibility of a disturbance in transmethylation in schizophrenia.[20] Subsequently, Hoffer and his associates administered niacin and niacinamide to chronic schizophrenic patients in the hope that these methyl acceptors would competitively inhibit other methylations. The clinical improvements which they saw [14] have not been confirmed.

Pollin et al [22] administered large doses of l-methionine and ordinary doses of iproniazid to chronic schizophrenic patients to learn whether possible increases in amounts of methylated amines would potentiate a schizophrenic process. The monoamine oxidase inhibitor (MAOI) was expected to slow amine catabolism, and it was felt that the methionine load might favor the formation of methylated compounds [15] by way of *S*-adenosylmethionine, shown by Cantoni [6] to play a crucial role in biological transmethylations. They reported that 4 of their 12 patients demonstrated a brief intensification of the psychotic state which could be interpreted as an exacerbation of schizophrenia. There were no reactions to MAOI or methionine alone initially, but more recently there has been an unconfirmed instance of similar behavioral changes in one strong reactor given methionine with or without MAOI.*

The present study was undertaken in an attempt to extend the series of "methionine reactors" in a double-blind clinical study and to compare the effects of another MAOI, isocarboxazid, with the previously employed iproniazid. In addition, an attempt was made to differentiate clinically a true intensification of the schizophrenic process from a superimposed toxic organic psychosis in those patients who demonstrated behavioral effects when given methionine plus MAOI.

Method

The study was carried out at Spring Grove State Hospital in Catonsville, Md.† Patients selected were males, aged 20-40 years, with unquestioned diagnoses of schizophrenia of two-ten years' duration. Individuals with medical or surgical illness, abnormal hepatic or renal function, organic brain syndrome, or gross mental deficiency were excluded.

The medications were coded and scheduled by a physician who was not a blind observer. Iproniazid and a placebo were supplied in identical form, as were isocarboxazid and its placebo.‡ The methionine was prepared in 0.5 gm tablets with a specially designed light enteric coating known to be stable in acidic gastric contents, but to dissolve readily in the small bowel, in order to avoid the effect of unpleasant eructations. Glycine was given as a "placebo" in identical form. Because of the characteristic odor associated with methionine ingestion, small amounts of methionine (50 mg) were included in the glycine tablets.

The following drug administration program was used:

1. All patients had been taking tranquilizers (phenothiazines) until the present study began, when they were replaced for three weeks with a specific placebo identical to the MAOI they would receive.

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* Rubel, Durell, and Kety, unpublished observations.

† Dr. Albert A. Kurland, Director of Research, Department of Mental Hygiene, Maryland, cooperated in this study. Mr. Kenneth McCusker and Mrs. Kester Johnson of the Spring Grove Research Staff gave assistance.

‡ Hoffman-LaRoche, Inc., supplied the medications.

2. Next, MAOI were given to replace the placebos. The dose of iproniazid (Marsilid) was 50 mg/70 kg per day, and that for isocarboxazid (Marplan) was 20 mg/70 kg per day, given (to the nearest 5 mg) as 10 mg tablets for four weeks.

3. After a week of MAOI alone, glycine was added to the regimen for one week.

4. Finally there followed a two-week period in which half the patients received methionine tablets the first week, and glycine the second week, and half received the amino acids in the reverse order. Amino acids were given at 20 gm/70 kg per day (to the nearest 0.5 gm) as 0.5 gm tablets, with a light enteric coating.

A thorough medical examination of each patient was performed at the start of the study. Serum glutamic oxaloacetic transaminase (SGOT) and urinalysis were performed frequently during the study. The effects of the MAOI's in most of the patients were estimated by determinations § of the ratio of urinary tryptamine: indoleacetic acid [18,25] on random specimens of urine at two weekly points with placebo and at two weekly points during MAOI administration.

Three physicians interviewed and examined the patients several times a week, recorded their observations, and filled out an RP scale.[23a] Nurses kept a log of patient behavior and completed weekly a Behavioral Adjustment Scale [8] and a Psychotic Reaction Profile [19] for each patient. At the end of the study all of these clinical data were evaluated independently without knowledge of the drug schedule, and later compared with the drug program to seek correlations between drug treatment and clinical impression of behavior.

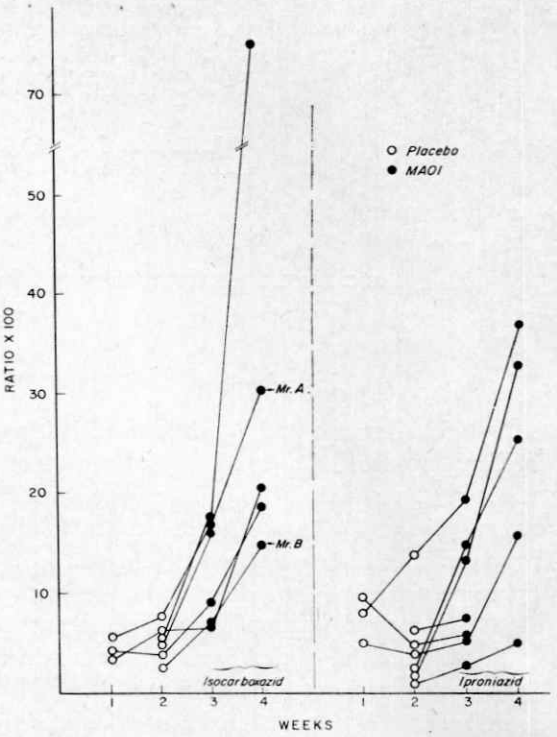
Results

Of the 25 patients who were selected for the study, 17 completed the full seven-week program. Of the eight who were discontinued, six refused to ingest the drugs, and two developed medical problems unrelated to the study. Of the 17 who completed the study, eight received iproniazid and nine, isocarboxazid.

Two instances of obvious behavioral change were noted by all observers during the study, and these manifestations were later found to have occurred when the patients were taking methionine plus isocarboxazid. The case summaries of these men, Mr. A and Mr. B, follow below.

During subsequent evaluation of the clinical data, all observers found one more patient who was noted to have some significant behavioral change in the week when he was given methionine and isocarboxazid (Mr. C).

In the remaining cases, the clinical changes were not remarkable and did not correlate with the drug schedule.



Effect of placebo and MAOI on ratio of tryptamine: indoleacetic acid in the urine of schizophrenic patients.

The data presented in the Figure demonstrate that both MAOI produced striking changes in the ratios of excretion of tryptamine:indoleacetic acid which fell in about the same range for both drugs. The excretion ratios for the two strong methionine reactors (Mr. A and Mr. B), and thus presumably the degree of MAO inhibition, were not significantly different from those of other nonreactors.

The finding that two patients were actually clinically better in the week after their reaction to methionine than at any other time in the study is difficult to assess, although it supports a similar impression noted by Pollin et al,[22] and Brune and Himwich.[4]

Case Summaries of Reactors to Methionine-MAOI

CASE 1.—Mr. A was a 22-year-old single white male who had been hospitalized for 3.5 years after the insidious development of an illness characterized by withdrawal, passive-aggression, preoccupation with fantasy,

§ Dr. Irwin J. Kopin, Chief of Section on Medicine of the Laboratory of Clinical Science, National Institute of Mental Health, NIH, Bethesda, Md, and his technical staff assayed patients' urine for tryptamine: indoleacetic acid.

and grandiose delusions. There was an uncertain history of auditory hallucinations. Diagnosis was schizophrenic reaction, chronic undifferentiated type. He was physically underactive, verbalized little, but possessed average intelligence. He presented a moderately obese, slovenly appearance, and complained bitterly of loneliness, hopelessness, and a discomfort in his head, blamed on electric convulsive therapy (ECT). At times he expressed grandiose delusions quietly. His affect was generally flat; he was mildly depressed and displayed infrequently childish delight in irritating other patients. His judgment and insight were impaired. On the second to fifth days of methionine ingestion he became restless, irritable, depressed, and complained of insomnia, dizziness, and anorexia and vomited twice. He felt "craziness" in his head; he feared that he would die, "disappear and go to heaven." On the sixth day he reported a disturbing nocturnal "vision" that he refused to discuss. He remained fully conscious, but at times poured forth grandiose delusions and ideas of reference. Later that day, he became more buoyant and aroused, with an active interest in himself and in communicating with others. In the week following methionine, this patient was clearly less psychotic than during any other time in the study.

CASE 2.—Mr. B was a 28-year-old single white male who had been hospitalized for 5 years after transfer by court order from a prison where he awaited trial for burglary. In jail, he had developed ideas of reference and influence, and experienced persecutory auditory hallucinations. He was preoccupied with ideas of organized accusation by prisoners and guards of sexual perversions, became angry and assaultive, and required physical restraint. At Spring Grove he became so calm and cooperative that for a time there was a difference of opinion regarding his diagnosis of schizophrenic reaction, paranoid type. He was mildly obese, neatly dressed, passive and isolated, but usually followed routine, and would speak pleasantly if addressed. He was rarely overtly psychotic. His affect was quite flat, and at times he seemed to be concealing inappropriate humor. His intelligence was borderline, and his judgment and insight poor. Under rehabilitation pressures he became apprehensive, irritable, and at times verbally abusive and overtly paranoid. There had been three short-lived attempts to promote him to outpatient status, and on one return he complained of auditory hallucinations again. After four days of methionine, Mr. B changed markedly. An inappropriate smile appeared; his thought associations loosened; he became extremely suspicious, and reported a plot against him. He described auditory (accusations of sexual perversions) and even visual hallucinations. At night he saw his parents hanging from a tree, and saw a partially nude woman in the halls; light from another building seemed to beckon him to participate in homosexual activities. In association with severe affective distress, his attention and memory span appeared somewhat impaired, and his orientation to person and to time were mildly distorted; however, he was quite conscious. He complained of insomnia and anorexia. For weeks after methionine ingestion, this patient remained quite disturbed, and frequently violent. Six weeks after methionine, and after four weeks of heavy chlorpromazine tranquilization, he began to show improvement.

CASE 3.—Mr. C a 39-year-old married white male had been hospitalized repeatedly for six years, always voluntarily, until his present involuntary admission nine months previously, following charges of child molestation. The patient interpreted this charge as a "frame-up by people out to get" him. He had had paranoid preoccupations for many years. Diagnosis was schizophrenic reaction, paranoid type. He was muscular and neatly dressed, of average intelligence; his speech had a childish, pleading quality, with a slight lisp. He complained of headache, insomnia, lack of concentration, anxiety, and had various somatic delusions. He used occasional neologistic speech. There was no history of hallucinations. His affect was blunted; he was slighly depressed; and there was impairment of judgment and insight. After five days of methionine, he felt "crazy" and wanted to see a doctor. He gave the interviewer the new impression of barely restrained assaultive impulses. His wife, for the first time during the study, also became alarmed, but could only say that the patient seemed very depressed and had "big staring eyes." The week after methionine, this patient seemed better than at any time during the study.

Comment

The present results appear to confirm those of Pollin et al,[22] who used methionine and iproniazid, as well as those of Brune and Himwich [4] who found psychotic exacerbations with methionine and isocarboxazid, and those of Alexander et al [1] who used methionine and tranylcypromine. Brune and Himwich [5] have also reported that betaine, another methyl donor, can be substituted for methionine to produce these clinical reactions.

A striking difference in the present findings from earlier studies is the low incidence of reaction to methionine (18%). There is no clear explanation for this fact, but several speculations are possible. The low incidence may reflect an effect of sampling, ie, the predominance of cooperative, placid, inactive cases. Possibly the patients were not brought to a basal state sufficiently free of extraneous drug effects (viz, phenothiazines). It is possible that the specially designated enteric coating was still too impermeable and led to poor absorption of the amino acid, and in fact at least two patients reported passage of tablets at stool. It is also possible that criteria for positive reaction were more strict than those applied previously, but most of the previously reported reactions were quite gross and unmistakable. Perhaps a large

series of cases must be collected before the incidence of reaction to methionine and MAOI is ascertained.

The tryptamine:indoleacetic acid excretion data support the prediction [7,23] that MAOI dosages were effective and equivalent. While it is attractive to speculate on the greater incidence of reactions with isocarboxazid, the small number of reactions does not permit a statistically significant conclusion at this time.

Baldessarini and Kopin [3] have recently demonstrated that large doses of l-methionine in rats result in significant increases in brain and liver levels of *S*-adenosylmethionine. Evidence of enzymatic *N*-methylation of the normal metabolites, tryptamine and 5-hydroxytryptamine, to their dimethyl derivatives has been found in mammalian tissue by Axelrod.[2] The same methylated products were shown by Szara [26] and Fabing [9] to have hallucinogenic properties under certain conditions.

Friedhoff has found 3,4-dimethoxyphenylethylamine in the urine of schizophrenics [11-13] and his results have been variously contradicted [21] or, more often, confirmed [17,24,27] in several laboratories. That this compound differs from mescaline only in lacking a 2-methoxy group, and that it seems to occur in schizophrenics to greater extent than in normals, has aroused a good deal of interest.

Thus, there is a considerable body of evidence to suggest the hypothesis that some abnormal methylated compound, perhaps an amine, may be produced endogenously in some patients manifesting a schizophrenic reaction, and may somehow be responsible for components of the clinical picture. However, such an hypothesis is little more than speculation at this point, and a great many questions remain to be answered.

Many of the cases studied in this and earlier investigations of the methionine effect manifested somatic reactions, with dizziness, nausea, and vomiting. The question has been raised whether the increase in psychotic symptoms is simply a result of such somatic discomfiture. Pollin et al [22] gave ammonium chloride orally to several schizophrenics, including those who had reacted to methionine, and noted gastrointestinal upset and acidosis comparable to that produced by methionine, but no exacerbation of psychosis. They also found that the substitution of tryptophan for methionine led to a reaction not unlike mild alcoholic intoxication, with light-headedness and increased verbalization; but even with this effect, no frank psychotic reaction occurred. On the other hand, it could still be argued that methionine may have its own specific neurotoxic effects, and further that the combination of MAOI plus methionine may have other toxic effects. In fact, the precise role of the MAOI in these reactions remains to be demonstrated more adequately. It is a well-known clinical observation that MAOI alone can produce disturbed behavior both in schizophrenic and in nonpsychotic individuals.

The effects of MAOI plus amino acids on normal controls have not been adequately studied. In a small number of normal men who were given methionine and iproniazid in doses that had produced psychotic episodes in schizophrenics, the only effect noted was similar to that of MAOI plus tryptophan in schizophrenics mentioned above.¶ There has been a suggestion that methionine plus MAOI might produce effects resembling those seen in schizophrenics, when given to nonschizophrenic psychiatric patients.[1]

It can be very difficult to distinguish manifestations of exacerbated schizophrenia from a toxic syndrome superimposed on schizophrenia.[7a] To make a considered diagnosis in the case of the methionine reaction, one must not only be cognizant of the characteristics of schizophrenia, of toxic psychosis, and of the state produced by drugs like lysergic acid diethylamide (LSD) and mescaline, but must also be prepared to consider complex combinations of their symptomatology in the same patient. A brain syndrome superimposed on a schizophrenic state may manifest itself quite differently from that in a previously nonpsychotic individual.

In the mental status examination, any single symptom may occur in either the toxic or the schizophrenic condition. Nevertheless, certain symptoms are more likely to appear in one condition than in the other, and the overall pattern of symptoms may be differentially significant. For instance, an unexplained abrupt change in

¶ Pollin, Cardon, and Kety, unpublished observations.

mental status, with a fluctuating and variable course, is suggestive of an organotoxic state.[13a]

There are various characteristic phenomena associated with classical toxic psychosis, such as mental clouding and confusion (altered state of consciousness), and defective intellectual functions. Yet, a grossly clear sensorium is commonly seen in reactions to psychotomimetic drugs. Restlessness is common in organic psychosis, and may or may not be a helpful differential point. Anxiety and lability of affect are also frequent in toxic states, but they occur too often in schizophrenia to be useful differentially. It is a commonly expressed clinical maxim that nonauditory, and particularly visual hallucinations, are more frequent in toxic psychoses. In the case of visual hallucinations produced by LSD and mescaline, Klüver [16] and Feinberg [10] have contributed several valuable points in distinguishing these from schizophrenic visual hallucinations. The analysis of delusional material is not helpful in separating the toxic from the schizophrenic condition, since either may involve delusions, and because the content of the delusions derives, in both cases, from individual underlying personality structure.[28]

There are few useful objective instruments for making the differential diagnosis considered here, but positive findings with physical methods, standard laboratory techniques, or certain psychological tests would, of course, favor the diagnosis of a superimposed toxic state.

In the presently cited three case histories, there are elements in two that are consistent with the diagnosis of a toxic condition: abrupt change in behavior following drug administration (a point that does not help in the present consideration), nausea and dizziness, and the addition of visual hallucinations to previously nonvisual hallucinations. On the other hand, the lack of delirium and the resemblance of behavior to previous disturbances are consistent with the diagnosis of schizophrenic exacerbation.

The behavioral changes noted in the three patients who reacted to a regimen of MAOI plus methionine are presented as additions to the series begun by Pollin et al. Although these data are compatible with the hypothesis that methylation may be related to the etiology of some of the manifestations in the schizophrenic reaction spectrum, it is impossible at this time to exclude a merely interesting toxic or pharmacologic phenomenon. The diagnostic issues in this area are extremely complex, and simple clear-cut interpretations are not readily found.

Summary

Of 17 chronic schizophrenic patients who ingested methionine and isocarboxazid, two became clearly more psychotic, and a third appears to have reacted less strikingly. None of the patients receiving iproniazid reacted to methionine. The effectiveness of MAO inhibition was demonstrated by assaying urinary excretion of tryptamine:indoleacetic acid. The attempt was made to differentiate between true exacerbation of schizophrenia and mere toxic psychosis, and the problems in making this differentiation were discussed. The present data are consistent with the hypothesis that a methylated amine is etiologic in some forms of schizophrenia, but much more work is necessary to investigate this possibility. A study of the effects of MAOI plus methionine in normal humans might be useful.

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Generic and Trade Names of Drugs

Methionine—Meonine, Methionine, Metione.
Isocarboxazid—Marplan.
Chlorpromazine—Thorazine.
Tranylcypromine sulfate—Parnate Sulfate.

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