CHAPTER 26

Studies on Mescaline XII: Effects of Prior Administration of Various Psychotropic Drugs

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In comparing the blocking action of different psychotropic drugs on the mescaline-induced state, chlorpromazine and trifluprom azine were found to be the most active, prochlorperazine and thiopropazate moderately so, while diethazine accentuated the mescaline response. Promazine and promethazine were ineffective, a finding concurring with that in clinical practice. The intramuscular injection of these drugs after mescaline did not influence the continuous fall of amino acids and eosinophils [1].

The halogen on the phenothiazine nucleus was felt to be related to the antipsychotic effect, since chlorpromazine was far superior to promazine. There was no apparent explanation, however, for the marked blocking activity of the nonpiperazine phenothiazines against mescaline as opposed to those with a piperazine side chain. This seemed to contradict the results in daily clinical practice, for halogenated piperazine derivatives have a more rapid action on hallucinatory syndromes than chlorpromazine; the latter is particularly effective in anxiety states.

Why do barbiturates block the mescaline-induced state completely yet have no direct or immediate action in the psychoses? Does mescaline simply produce a biochemical anxiety stress[2] which can be neutralized by any sedative agent? Could the prior administration of some psychotropic drugs inhibit the mescaline-induced state in a fashion analogous to their clinical activity? If so, this might serve as a simple screening device for new drugs [3].

THE SETTING

The patients chosen for this study were treated in the research division ward of Manhattan State Hospital, a 3000-bed institution

of the New York State Department of Mental Hygiene. The ward has 55 acute and chronic female patients, most of them schizophrenic, and is run along the principles of a therapeutic community [4, 5]; all patients are fully aware of its particular nature. The staff carries on various research activities and, in addition, performs the hospital service functions.

MATERIALS AND METHODS

There were 39 trials in 38 patients (Table I) receiving a drug or saline followed by mescaline or saline. They had not been taking any medication for at least ninety-six hours before and were fasting on the morning of the test. The following compounds administered intramuscularly were unknown to the observer: 50 mg of chlorpromazine (five patients), 200 mg of diethazine (seven patients), 250 mg of Sodium Amytal (six patients), 20 mg of amphetamine* (eight patients), 5 mg of haloperidol (five patients), 3 mg of thioperazine (five patients), and 5 cc of physiological saline solution (three patients). One-half hour afterwards 500 mg of mescaline sulfate dissolved in 20 cc of physiological saline was injected intravenously. Saline (20 cc) was substituted for mescaline in the controls.

Before a patient received mescaline, she was told: "You will have a test once or, perhaps, more than once, depending on the

*d,l-amphetamine sulfate.

TABLE I

Clinical Diagnoses

Diagnosis	No. Cases
Schizophrenia	
Paranoid	15
Catatonic	6
Mixed	6
Simple	2
Hebephrenic	1
Psychoneurotic	6
Manic-Depressive	2
Total	38

results. Tomorrow I will give you an injection and you will simply tell me how it makes you feel. We will also take blood a few times. I will stay with you all the time. If you have any questions, you can ask me now or talk with the other patients who have already had the test. But whatever you hear, remember that nobody reacts exactly the same way."

The immediate effects of the drugs (or saline) were considered as either (1) producing drowsiness or (2) being ineffective. The clinical reactions to mescaline were observed during four hours and tabulated under four headings: (1) verbal, (2) motor, (3) neurovegetative, and (4) perceptual. The reactions in each group were graded as either marked, moderate, or mild. They were termed marked (3+) when the mescaline effects were present at least two-thirds of the observation period, moderate (2+) when the symptoms lasted more than one-third and less than two-thirds of the four-hour observation time, minimal (1+) when the symptoms occurred over a duration of time totaling less than 75 minutes. Appraisal of the total response was made by the sum of the separate reactions. In this way, unequal reactions in any one or all of the above categories were taken into account. Where the additive scores of all four groups totalled 4+ or less, the grading was one of a total mild response. A total moderate response was 5+ to 8+, and more than 8+ constituted a total marked response.

All patients were interviewed the next day to obtain additional information or to clarify the meaning of some ambiguous findings.

RESULTS

The immediate effect of a single dose of chlorpromazine produced drowsiness in four of five patients. Diethazine gave the same effect in four of seven patients, and Sodium Amytal in two of six. Amphetamine increased the verbal productivity in seven of eight patients. The other drugs were without effect.

Chlorpromazine proved to be the most effective inhibiting agent of the mescaline-induced state (Table II). There were four marked responses in the diethazine group. These patients had a very severe reaction to mescaline in the verbal, motor, and perceptual spheres.

There were one marked, five moderate, and two mild responses in the amphetamine group. Sodium Amytal had little effect upon the sequence of events in five of six patients. The saline sample (three patients) was too small to allow any conclusions.

TABLE II

Response to Mescaline According to the Preinjected Blocking Agents (39 trials in 38 patients)

Blocking Agent	Intensity of Response			Total No. Cases
	Mild	Moderate	Marked	
Chlorpromazine	4	1	0	5
Thioperazine	0	4	1	5
Haloperidol	1	4	0	5
Diethazine	2	1	4	7
Saline	1	1	1	3
Amytal	1	2	3	6
Amphetamine	2	5	1	8

The neurovegetative reactions were minimal with chlorpromazine, haloperidol, and in four of five patients receiving thioperazine but were moderate or marked with amphetamine, diethazine, Sodium Amytal and saline. Perceptual changes were absent in all cases pretreated with chlorpromazine and thioperazine but were present to varying degrees in the others. The changes were not always verbalized but could be inferred from the patient's behavior. When a mute subject lengthily examined her hand, turning it around with a bewildered look, it was interpreted as a perceptual change. The following day's interview always confirmed the clinical observations.

It made little difference for the end result with chronic schizophrenic patients if a neuroleptic or other drug was given (Table III). The schizophrenic patients in remission showed one marked and five moderate responses with a neuroleptic, while there were six marked and five moderate responses with nonneuroleptics.

The blocking effect produced by the injection of a drug before mescaline was much less pronounced than when given afterwards. A complete block was never obtained, and even with a minimal response some mild autonomic changes were noted during the first half-hour. The duration and intensity of the mescaline-induced

TABLE III

Response to Mescaline According to Diagnostic Groups and Comparing the Action of Preinjected Neuroleptic and Nonneuroleptic Substances

	Mild		Moderate		Marked	
Diagnostic Groups	Neuroleptic	Nonneur.	Neuroleptic	Nonneur.	Neuroleptic	Nonneur.
Acute schizophrenia	0	1	1	2	0	0
Remitted schizophrenia	1	1	5	5	1	6
Chronic schizophrenia	3	3	0	1	0	1
Psychoneurosis	1	1	3	0	0	1
Manic-depressive psychosis	0	0	0	1	0	1
Total (38 patients)	5	6	9	8	1	9

state were decreased in general, and after an hour or so the response was already waning. There was one marked response with a neuroleptic blocking agent* in 15 cases, whereas nine such responses occurred among 23 patients given other drugs. This was in distinct contrast to the observations made when mescaline was given alone; the one-hour postmescaline period corresponded with the appearance of varied and intense signs and symptoms [3].

With the prior administration of a neuroleptic, instead of the sharp verbal and motor expressions of anxiety and discomfort one frequently heard complaints such as, "This whole thing is boring... it is too long...I wish I could be back on the ward." It was necessary to terminate the mescaline-induced state with the aid of chlorpromazine only once because of uncontrollable symptoms, when a neuroleptic was used for initial blocking action. On the other hand, this was done four times with diethazine, twice each with saline and amphetamine, and once with Amytal.

*Chlorpromazine, thioperazine, and haloperidol.

DISCUSSION

While we were unable to assert definitely that diethazine aggravated the response to mescaline (since the summed action of both drugs was being observed), the evidence is very suggestive, inasmuch as four of the ten marked responses occurred in this group.

Amphetamine did not enhance the mescaline-induced state, with two mild, five moderate, and one marked response. When four of these patients received saline-mescaline in a third series of trials, three had identical reactions (moderate), while the fourth had a severe response.*

It has been indicated elsewhere that the clinical state induced by mescaline is neither an intoxication, a neurosis, nor a psychosis but a state of being in which the clinical spectrum runs from sleep to murderous rage and from normality to thoroughly disorganized states [6]. Schizophrenic subjects react to mescaline in a manner about inversely proportional to the length of their illness [7]. It is difficult to attribute the results in an acutely ill psychotic subject to either the drug or the illness. When the drug is given in a phase of remission, the psychosis is reactivated for the test period; administered to a chronic schizophrenic subject, it hardly produces any reaction. Eight patients had chronic schizophrenia (average duration of present hospitalization 47.1 months), and six of these had a mild response. Twenty-two belonged to the schizophrenic group in remission (average duration of present hospitalization 4 months), and of these two had a mild reaction as opposed to seventeen with a moderate or marked response (Table III).

There were five moderate responses with neuroleptic and nonneuroleptic drugs in the remitted schizophrenic group. Since the nonneuroleptic compounds should not have had an inhibitory effect upon the mescaline-induced state, the material was analyzed further. Three of the group having had a moderate reaction received amphetamine before mescaline. Biochemical studies have shown that intravenous mescaline caused an immediate fall in the level of ninhydrin-positive substances, and significance was achieved by one-half hour [2]. The fall of ninhydrin-positive substances and the intensity of the clinical reactions were correlated; the levels of the former fell as the mescaline-induced reaction became more intense. Immediately following amphetamine there was a rise in these levels,

*This was not the same patient who had a marked response in the original trials.

while the fall after mescaline was delayed, not attaining significance until two hours afterwards [3]. In view of these findings and as suggested by the clinical results, it can be inferred that there is some biochemical antagonism between amphetamine and mescaline.

The neurovegetative signs and clinical reactions with amphetamine were dissociated, with the former moderate to marked and the latter mild to moderate. This suggests that the autonomic reactions function independently of the cortical responses in this case.

What could be the nature of the mescaline stress? In schizophrenia, mescaline generates anxiety as the foremost symptom and other emotions are noticeably absent. The anxiety could result from the patient's changed apperception of the world and his body. The schizophrenic subject may view this as a destructive event with loss of and/or transformation of the body or its parts. Because he does not know how far these changes will proceed, terror becomes more and more marked. The intense anxiety leads one to wonder if the patient is not equating them to changes in the world and self. Theoretically, if this goes far enough, it could lead to symbolic death, explaining to some degree the severe psychological and motor reactions with mescaline. The neurotic patients, on the other hand, recognize the boundaries of the mescaline-induced state, and their anxiety does not have the devastating effects seen with schizophrenic patients. The former ofttimes tend to describe their reaction as "thrilling."

Perceptual changes were found only once with chlorpromazine and thioperazine. The presence of perceptual distortions is indicative of a disorganization of those central functions subserving man's relation in time and space. Mescaline seems to remove the normal protective filter mechanisms that prevent the organism from being overwhelmed by a flood of sensory stimuli. When these restrictions no longer exist, there is a state of confusion with perceptual discrimination no longer possible. Thus, like the patients of Davie and Freeman [8], they confused various peripheral stimuli. ("There is my father in the doorway. He'll kill me.") The patient responds with the autonomic nervous system to the drugs since this is probably a more primitive response, but when protected (chlorpromazine and thioperazine) the reaction is stopped. Where the contrary is true (diethazine, Amytal, and saline), the autonomic reaction is followed by the symptoms due to mescaline. Chlorpromazine and thioperazine, which protect against the perceptual changes due to mescaline, do the same in clinical practice.

Our data yield no reason for the greater clinical effectiveness of piperazine phenothiazines as opposed to their decreased ability to block mescaline. The measurement of the ninhydrin-positive substances during the mescaline-induced state seems to offer a more reliable index of the drug's clinical activity than the clinical responses. As our studies continue with increased numbers in each group, some of these questions will probably be answered.

The mescaline stress has some specificity with regard to those compounds that will block the different symptoms. Sodium Amytal, with its sedative properties, was ineffective, yet chlorpromazine, also sedative but antipsychotic, was very effective. It is difficult to say why intravenous barbiturates administered after mescaline will block its effects [9] while prior intramuscular injection does not. The route of administration may be a factor, and further studies will test this.

In view of the relationship between the blocking effects of different drugs on the induction of the mescaline-induced state and their correlation with results in clinical psychiatric practice, we are led to believe that the drug-induced condition can be considered as an analogy of the endogenous psychosis without at the same time suggesting any specificity. Only continued investigation will either demonstrate the validity of such a hypothesis or show it to be a fallacy [10].

SUMMARY AND CONCLUSIONS

1. Chlorpromazine, thioperazine, haloperidol, Sodium Amytal, d,l-amphetamine sulfate, diethazine, and saline were administered in 39 trials to 38 patients before mescaline. Chlorpromazine was most potent, followed by thioperazine and haloperidol, in blocking the induction of the mescaline-induced state.

2. There was little differentiation in the end result with a chronic schizophrenic subject if a neuroleptic or other drug was given. On the other hand, for the schizophrenic patients in remission, the neuroleptics were able to block most of the symptoms, while the other drugs could not.

3. There is a certain antagonism between amphetamine and mescaline, which is supported by the biochemical and clinical data.

4. Some theoretical considerations have been made about the nature of the mescaline stress.

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Discussion by Sidney Merlis, M.D., F.A.C.P.

The data presented by Drs. Rajotte and Denber and Miss Kauffman are at once provocative and novel. To my knowledge, it is one of the first attempts using a well-defined consistent research design to establish an answer to a question which has been in the minds of all of us whose interest and work have had to do with the psychotomimetic drugs. Much has been written about mescaline and LSD-25 and related compounds. Reports have ranged from basic well-prepared physiological reports to fanciful clinical reports suggesting promising clinical and therapeutic activity which for the most part has been disappointing.

It is only in very recent times that these drug effects have been removed from the category of being considered as producing a schizophrenic-like condition and are now more accurately described as a toxic state. The early hopes and expectations that researchers felt with the introduction of these compounds have to a very large extent not materialized. The compounds have not been unequivocally accepted as therapeutic agents. They have not fulfilled the promise of giving us major insight into the dynamics and physiology of schizophrenia. Dr. Denber and his associates are among the few investigators who have continued their clinical research activities with mescaline and over the past few years have significantly contributed to our

understanding of the physiological and psychodynamic correlations relative to this drug-induced state.

The work involves a rather interesting concept, namely, the attempt to correlate clinical effectiveness of various psychotropic agents to alterations of the mescaline response. It is an effort to present information which is so necessary to bridge the gap that exists between the use of psychotomimetic drugs as experimental agents and the psychotic disturbances that we see clinically in our patients.

There are several points in this report which require some comment. In essence, the data represent an effort to study the psychotropic drug effect by means of a human bioassay method utilizing mescaline as the standard. Pharmacologists are ordinarily reluctant to use bioassay methods unless no other means are available. To this extent the procedure is justified in the paper just read. The criteria, however, for reliability of any bioassay method, because of its inherent variability, can only be discounted by adequate experimental trials and the use of suitable statistical methods. This the authors have indicated will eventually be done. The final evaluation of the suitability of this procedure must await additional trials.

The obstacles of natural patient variability and diverse clinical responses to so complex a drug as mescaline is not so easily discounted. Subjects who receive mescaline show a great variety of reactions to the drug. What is even more significant and to a large extent not too often described is that individual subjects show different responses to mescaline on different days. To further complicate the picture, it is known that various psychotomimetic drug antagonists when used alone can also show highly individualized and equally diverse reactions.

Further considerations require a more specific clarification of the distinction between a true pharmacological antagonism (blocking) and actual suppression. We must differentiate more precisely between evidence of specific blocking with rather modest doses of a compound and a masking or suppression secondarily related to impaired awareness in heavily premedicated individuals. It would appear, for example, that the barbiturates act by such a suppressive action.

While the psychological changes in the mescaline state are less easily predictable and thus more subject to errors in individual evaluations, the physiological reactions are somewhat more characteristic and thus may be used to some degree as a parameter of drug effect. One must always remember that the physiological responses are compatible with a general bodily response to external stress and are not specific for mescaline alone.

Lastly, I would like to point out that the thesis presented by the authors is an analogical argument. Namely, the program of research here described is inferring a further degree of resemblance from an already observed degree. The doctrine of signatures formerly so prevalent in therapeutic medicine is being implied with the psychotomimetic drugs. In the past, walnuts were prescribed for brain diseases because they physically so resembled a brain and bear grease was used for baldness because bears are so hairy. Mescaline has been used in the same manner because of the seeming resemblance of its effect to schizophrenia. Dr. Denber and his associates are acutely aware of the problems relative to this type of research. He uses good judgement and considerable restraint in presenting his data. He is particularly aware of the limitations imposed, and because of this awareness the data presented must be considered as most meaningful. I, for one, shall look for additional reports in this most interesting series of studies.