

Glucose Tolerance in Man during Chlorpromazine Therapy

Leo Waitzkin, M.D., Brockton, Massachusetts

SUMMARY

Neither brief nor long chlorpromazine therapy appears to impair carbohydrate tolerance in hospitalized, mentally ill men under fifty years of age, as measured by a 100-gm., three-hour, oral glucose tolerance test. *DIABETES* 19:186-88, March, 1970.

In 1966, observations were reported suggesting an unusually high prevalence of previously unknown diabetes in a mental hospital.¹ It was recommended that further investigation be conducted to determine if prolonged phenothiazine therapy had a diabetogenic influence.

The literature concerning chlorpromazine's effect on man's carbohydrate tolerance is difficult to evaluate. In animals, a large dose of chlorpromazine has a hyperglycemic effect.²⁻⁸ Results of acute experiments in man are conflicting.⁹⁻¹¹ A spatter of undocumented statements, sporadic case records and reports allege that chlorpromazine may impair man's carbohydrate tolerance after as little as ten days and after as long as several years of therapy, with daily dosage as modest as 150 mg.¹²⁻¹⁷ With diabetes common and its natural course variable, with chlorpromazine therapy widely used and often followed by considerable weight gain,¹⁸ the occurrence or worsening of diabetes during such therapy may be coincidental or related to added weight. The presently reported study investigated man's carbohydrate tolerance during brief and prolonged chlorpromazine treatment.

SHORT-TERM STUDIES

I. MATERIAL AND METHOD

As a result of the aforementioned survey and the continuing search for diabetes among the in-patient population at this Veterans Administration Hospital in Brockton, Massachusetts, it has been possible to classify a large proportion of the patients as diabetic or nondiabetic according to the criteria of Fajans and Conn.¹⁹ Patients were called diabetic if, on each of two consecutive 100-gm. oral glucose tolerance tests, they had a

combination of venous blood glucose levels, by Somogyi-Nelson method,²⁰ of 160 mg. or more at one hour, 140 mg. or more at one-and-one-half hours, and 120 mg. or more at two hours.

Any patient was eligible for this investigation if he was on no drug known to be diabetogenic and had received no phenothiazine derivative for at least five weeks preceding study. An eligible subject was taken for study or excluded solely on his psychiatrist's readiness or unwillingness to discontinue all current drug therapy directed at his psychiatric state and to substitute chlorpromazine orally, 200 mg. or more daily, for a minimum of three weeks. The first twelve diabetics and twelve nondiabetics so accumulated were given glucose tolerance tests before and after a period of chlorpromazine therapy. Duration of therapy for most subjects was three weeks; for the rest, four to ten weeks. Daily dosage for the diabetics ranged from 200 to 550 mg.; mean, 260; median, 200 mg. For nondiabetics the range was 200 to 900 mg.; mean, 425; median, 300 mg. Mean ages of the two groups were not significantly different and no significant weight change occurred between tolerance tests (table 1).

A 100-gm., three-hour oral glucose tolerance test was performed under controlled supervision, after three days of supervised, recorded, adequate dietary intake consisting of the regular hospital diet plus 100 to 150

TABLE 1
Age and weight of subjects

		Diabetics (N = 12)	Nondiabetics (N = 12)
Age (yrs.)	Range	38-64	33-73
	Mean	48.8	43.6
Weight (lbs.)	Before CPZ	187±9	172±11
	After CPZ	188±8	174±11

gm. of glucose in orange juice daily. NPH insulin, started in one case long before the study, was continued through the course of the evaluation, but was not given on the morning of the test. Tolbutamide, being received by two subjects, was stopped for the four days preceding each tolerance test. Results before and after treatment with chlorpromazine were analyzed by *t* tests for each time point, with each subject serving as his own control.

From the Veterans Administration Hospital, Brockton, Massachusetts 02401.

2. RESULTS

In the diabetic group, after chlorpromazine, mean blood glucose level at one-and-a-half hours was lower ($p < .05$). At all other time points, the mean glucose levels of diabetics and nondiabetics were not significantly different after therapy (table 2).

TABLE 2
Mean blood glucose, before and after chlorpromazine

Blood-glucose mg./100 ml.	Diabetics (N = 12)		Nondiabetics (N = 12)	
	Before CPZ	After CPZ	Before CPZ	After CPZ
Fasting	101	101	79	75
1 hr.	211	200	133	132
1½ hr.	231	206	115	120
2 hr.	215	196	104	108
3 hr.	160	153	80	72

LONG-TERM STUDIES

I. MATERIAL AND METHOD

Part of the data herein analyzed was collected in the course of a survey for unknown diabetics at this hospital.¹ That survey was begun by listing all ambulatory male patients under age fifty who were present in the hospital on a given day. Of 549 listed, any with the following were eliminated: known diabetes (4.4 per cent of the list), disorders of the thyroid, pituitary or adrenal glands, active pulmonary tuberculosis or other debilitating illness, gastrectomy or gastroenterostomy. Others were lost through discharge before they could be studied. As a result, 359 (65 per cent) of the 549 were investigated.

Of these 359, 104 were receiving chlorpromazine and 189 mellaril at the time their glucose tolerance tests were done. They represented 66 per cent and 74 per cent of all patients on chlorpromazine or mellaril, respectively, who had been initially listed for the survey. At testing, duration of chlorpromazine therapy ranged from less than one month to ninety-two months; mean, fifteen; median, eleven months. Range of average daily dose was 75 to 2,076 mg.; mean, 680; median, 627 mg. Duration of mellaril therapy ranged from less than one month to thirty-five months; mean, fifteen; median, seventeen months. Range of average daily dose was 88 to 1,416 mg.; mean, 463; median, 451 mg. After these two groups were tested, a control group was accumulated of fifty-eight newly hospitalized, mentally ill men who were ambulatory, under age fifty, had never received phenothiazine drugs, and had never been known to have diabetes.

All subjects received the regular hospital diet, which averaged 2700 calories daily and contained 100 gm. of protein and 300 gm. of carbohydrate. They were given

a 100-gm., three-hour oral glucose tolerance test and venous blood glucose levels were determined by the Somogyi-Nelson method. Results were classified by two sets of criteria. By the Fajans and Conn criteria, a combination of 160 mg. per 100 ml. or above at one hour and 120 mg. per 100 ml. or above at two hours was abnormal.¹⁹ By the criteria of the U.S. Public Health Service, results were abnormal when any three or more of the following values, or the fasting and three-hour combination, were met or exceeded: fasting, 110 mg. per 100 ml.; one hour, 170; two hours, 120; three hours, 110 mg.²¹

The groups were compared by age and weight (Student's *t* test); by psychiatric diagnosis and family history of diabetes (chi square test). Mean age of the chlorpromazine group was thirty-six years; of the mellaril, thirty-eight; and control, thirty-nine years. The latter two were not notably different.

In a classification of group members as overweight, underweight or desirable,²² 42 per cent of the chlorpromazine subjects, 36 per cent of the mellaril and 16 per cent of the control were overweight 20 per cent or more (table 3). Both phenothiazine groups were significantly heavier than the control ($p < .025$).

TABLE 3
Distribution of groups by weight

	Chlorpromazine		Mellaril		Control	
	Num- ber	Per cent	Num- ber	Per cent	Num- ber	Per cent
Desirable weight	10	10	25	13	15	26
Per cent overweight:						
1- 9	22	21	39	20	11	19
10-19	21	20	44	23	12	21
20 or more	44	42	68	36	9	16
Underweight	7	7	13	7	11	19

Almost 90 per cent of the chlorpromazine and mellaril groups had chronic schizophrenia—a significantly greater proportion than the 12 per cent in the control ($p < .001$) (table 4).

TABLE 4
Distribution of groups by psychiatric diagnosis

	Chlorpromazine		Mellaril		Control	
	Num- ber	Per cent	Num- ber	Per cent	Num- ber	Per cent
Schizophrenia, chronic	92	88	168	89	7	12
Chronic brain syndromes	11	11	10	5	8	14
Other functional disorders	1	1	11	6	43	74

There was a positive family history of diabetes in 27 per cent of the chlorpromazine group, 29 per cent of the mellaril and 34 per cent of the control group. Differences between groups were not significant.

2. RESULTS

By Fajans and Conn criteria, glucose tolerance results were abnormal in 16 per cent of the chlorpromazine group, 21 per cent of the mellaril and 10 per cent of the control group. These percentages were not significantly different from each other (chi square tests). Comparison of the groups by age showed the frequencies of abnormal results not to be notably different in the fourth and fifth decades. Data of the third decade were insufficient for statistical analysis (table 5).

TABLE 5

Abnormal glucose tolerance results (Fajans-Conn criteria), by group and age

Age (yrs.)	Number	Abnormal GTT	
		Number	Per cent
Chlorpromazine			
20-29	15	2	13
30-39	59	8	14
40-49	30	7	23
Total	104	17	16.3
Mellaril group			
20-29	16	0	0
30-39	98	15	15
40-49	75	24	32
Total	189	39	20.6
Control group			
20-29	6	1	17
30-39	20	1	5
40-49	32	4	13
Total	58	6	10.3

Compared by weight class, chronic schizophrenia and family history of diabetes, the prevalences of abnormal tolerance results in the chlorpromazine, mellaril and control groups were not significantly different.

By USPHS criteria, prevalences of abnormal glucose tolerance results in the chlorpromazine, mellaril and control groups were not significantly different (table 6).

TABLE 6

Abnormal glucose tolerance results, by USPHS criteria

Group	Number	Abnormal GTT	
		Number	Per cent
Chlorpromazine	104	6	5.8
Mellaril	189	15	7.9
Control	58	1	1.7

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