Relation of hypermagnesaemia to activity and neuroleptic drug therapy in schizophrenic states

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SUMMARY In a study designed to explain conflicting reports of hypermagnesaemia in schizophrenia, significantly higher concentrations of plasma-magnesium were found in phenothiazine-treated schizophrenic women than in normal women of the same age. This did not apply to men. Magnesium levels were inversely related to motor activity in untreated chronic schizophrenic men in hospital as well as in patients of both sexes receiving butyrophenone or phenothiazine derivatives. The magnesium concentration fell significantly when institutionalized schizophrenic and non-schizophrenic men were placed on neuroleptic medication. It is concluded that age, sex, pharmacotherapy, and level of activity all influence the metabolism of magnesium in schizophrenic subjects.

Significantly elevated magnesium concentrations in the plasma of schizophrenic subjects have been reported in some studies (Katzenelbogen and Snyder, 1943; Cade, 1964; Brackenridge and McDonald, 1969) but not in others (Gottfried and Willner, 1949; Masiak and Bernaskiewicz, 1965; Seal and Eist, 1967). The significance of these conflicting reports is unclear for two sets of reasons: firstly, substantial differences in the clinical criteria required for a diagnosis of schizophrenia exist; secondly, a large number of variables are known to affect magnesium levels (Walser, 1967). These facts make a study of any relationship between the two sets of factors possible only by defining the clinical criteria precisely and by controlling as many as possible of the variables known to affect magnesium levels.

We present here the results obtained over a three-year period on patients defined according to the criteria indicated below.

SUBJECTS AND METHODS

SUBJECTS All psychiatric patients were free from known physical disease. Diagnostic criteria and clinical notes have been reported previously for patients with acute and chronic schizophrenia (Brackenridge and Jones, 1968; Whittingham, Mackay, Jones, and Davies, 1968; Brackenridge and McDonald, 1969; Jones, Davies, Buckle, Hanna, and Pikla, 1970). Acutely-ill psychotic cases had been recently admitted to a hospital ward at the time of blood collection, while chronic patients had been confined to a mental hospital after an episodic

course of illness. The criteria for diagnosis were: the presence of cardinal symptoms such as passivity-feelings or schizophrenic thought-disorder, a constellation of symptoms constituting one of the Kraepelin (1919) subtypes of schizophrenia or symptoms intermediate between two Kraepelin sub-types.

A mixed group of chronically-ill, non-schizophrenic hospital patients consisted of nine with Korsakoff's psychosis, eight with general paralysis of the insane, eight with mental retardation, five with chronic brain syndrome, four with alcoholic dementia, two with personality disorder, and one each with endogenous depression, Huntington's chorea, post-encephalitic and post-traumatic states. Twenty-one of these 40 were receiving drug treatment at the time of blood collection.

All patients were matched with normal control subjects for sex and within three years for age. Details have been given elsewhere (Brackenridge and Jones, 1968).

METHODS Male chronic schizophrenic patients were assessed for motor, social, and total activity by means of the Venables (1957) scale, and for structural preservation of speech, extent of hallucinations, delusions, ideas of reference, general information, and orientation for time and place using the scale of Harris, Letemendia, and Willems (1967). Venous blood samples were drawn into tubes containing lithium heparin. Plasma-magnesium determinations were carried out by atomic-absorption spectrophotometry (Willis, 1960; Brackenridge and McDonald, 1969).

Standard statistical methods were used, including Student's *t* test for independent and paired samples, product-moment and partial correlation coefficients, and analysis of variance. Calculations were performed on an Olivetti Programma 101 computer.

RESULTS

NORMAL SUBJECTS The mean ($\pm$ SD) plasma-magnesium concentration in 86 healthy men aged 37.6 $\pm$ 18.1 years was 2.07 $\pm$ 0.18 mg/100 ml., while the mean in 60 healthy women aged 43.9 $\pm$ 23.8 years was 2.08 $\pm$ 0.18 mg/100 ml. Values were distributed normally in each group. A significantly positive correlation with age was found in females ($r = 0.43$, $P < 0.001$) and in both sexes combined ($r = 0.28$, $P < 0.001$), but not in males ($r = 0.16$, $P > 0.1$).

SCHIZOPHRENIC PATIENTS The magnesium levels in schizophrenic patients undergoing phenothiazine medication are presented in Table 1. The mean concentrations in the men were not significantly higher than those in their control groups, whereas the female groups were appreciably hypermagnesaemic. Normal distribution curves were observed throughout.

Significant correlation coefficients between plasma-magnesium concentration and age were found in chronic female schizophrenic patients ($r = 0.44$, $P < 0.05$), all chronic patients (0.53 , $P < 0.001$), all female patients (0.44 , $P < 0.001$), and all patients (0.36 , $P < 0.001$). Although a sex-effect appears to operate in Table 1, the mean ages of the male and female groups differ appreciably. It was possible to match 18 acutely-ill patients of each sex closely for age. The mean plasma-magnesium level in the men (2.04 $\pm$ 0.22 mg/100 ml.) was lower than that in the women (2.11 $\pm$ 0.23 mg/100 ml.), but not significantly so. When these 18 pairs were supplemented by an additional 17 pairs of chronic schizophrenic patients, the male levels (2.06 $\pm$ 0.19 mg/100 ml.)

became significantly lower ($P < 0.05$) than the female levels (2.17 $\pm$ 0.23 mg/100 ml.). This effect did not apply to 38 pairs of healthy control subjects whose matched ages varied from 15 to 74 years. The mean concentration for normal men (2.05 $\pm$ 0.15 mg/100 ml.) did not differ from that for normal women (2.05 $\pm$ 0.18 mg/100 ml.).

RELATION OF PLASMA-MAGNESIUM LEVELS TO ACUTE SCHIZOPHRENIC SYMPTOMS Magnesium concentrations could not be related to the following factors in acutely-ill patients being treated with phenothiazine derivatives: age, length of history, number of episodes, Kraepelin subtype, or particular symptoms such as passivity-feelings, presence or absence of thought-disorder, hallucinations, delusions, ideas of reference, and severity of symptoms. The age at onset of symptoms was significantly higher for women (30.8 $\pm$ 11.1 years) than for men (21.0 $\pm$ 5.9 years) ($P < 0.001$). The mean duration of illness was 40 months in each case.

MAJOR TRANQUILLIZERS The effects of two neuroleptic drugs were examined on two groups of hospitalized schizophrenic males matched with respect to age and type of symptoms. Treatment was suspended for six weeks, after which blood was collected from each participant. Twenty then received a phenothiazine derivative (trifluoperazine, 11.5 mg twice daily) and 20 were placed on a butyrophenone derivative (methylperidol, 14 mg twice daily). After seven weeks of this treatment blood samples were again taken. Plasma-magnesium concentrations were significantly lower ($P < 0.01$) after trifluoperazine therapy (2.13 $\pm$ 0.18 mg/100 ml.) than before (2.31 $\pm$ 0.21 mg/100 ml.). They were also

TABLE 1
PLASMA-MAGNESIUM LEVELS IN TREATED SCHIZOPHRENIC AND CONTROL SUBJECTS

Diagnostic group	Males			Females			Both sexes		
	Patients	Controls	P	Patients	Controls	P	Patients	Controls	P
Acute schizophrenia:									
Number	30	30		30	30		60	60	
Mean age $\pm$ SD (yr)	23.6 $\pm$ 6.3	23.6 $\pm$ 6.5		34.7 $\pm$ 12.8	34.5 $\pm$ 12.9		29.1 $\pm$ 11.5	29.1 $\pm$ 11.6	
Mean Mg $\pm$ SD (mg/100 ml.)	2.08 $\pm$ 0.22	2.04 $\pm$ 0.16	NS	2.16 $\pm$ 0.24	2.02 $\pm$ 0.16	<0.01	2.12 $\pm$ 0.23	2.03 $\pm$ 0.16	<0.01
Chronic schizophrenia:									
Number	40	40		25	25		65	65	
Mean age $\pm$ SD (yr)	45.2 $\pm$ 9.0	45.3 $\pm$ 9.5		68.8 $\pm$ 8.5	68.4 $\pm$ 9.2		54.3 $\pm$ 14.5	54.2 $\pm$ 14.7	
Mean Mg $\pm$ SD (mg/100 ml.)	2.11 $\pm$ 0.17	2.05 $\pm$ 0.18	NS	2.36 $\pm$ 0.23	2.18 $\pm$ 0.16	<0.01	2.21 $\pm$ 0.23	2.10 $\pm$ 0.18	<0.01
Both schizophrenic groups:									
Number	63	63		51	51		114	114	
Mean age $\pm$ SD (yr)	36.6 $\pm$ 13.7	36.3 $\pm$ 14.3		49.8 $\pm$ 21.0	49.6 $\pm$ 21.2		42.5 $\pm$ 18.5	42.2 $\pm$ 18.8	
Mean Mg $\pm$ SD (mg/100 ml.)	2.09 $\pm$ 0.19	2.05 $\pm$ 0.17	NS	2.25 $\pm$ 0.26	2.09 $\pm$ 0.19	<0.001	2.16 $\pm$ 0.24	2.07 $\pm$ 0.18	<0.001

significantly lower ($P < 0.01$) after methylperidol therapy (2.10 ± 0.16 mg/100 ml.) than before (2.28 ± 0.19 mg/100 ml.). The levels after each type of treatment did not differ significantly from each other.

ACTIVITY Patients treated for acute schizophrenic episodes were rated for motor activity by observation or from study of their clinical records. Because overactive and underactive persons could be assessed with most precision, the plasma-magnesium concentrations of these two groups were compared and the remainder of average or uncertain activity were discarded. The mean level of seven hyperactive subjects (1.96 ± 0.24 mg/100 ml.) was less than that of 22 withdrawn subjects (2.15 ± 0.24 mg/100 ml.) but the difference fell short of significance. When treated patients with chronic schizophrenia were rated in the same way and combined with the results of the acutely-ill patients, the mean level of seven hyperactive persons (1.96 ± 0.24 mg/100 ml.) was significantly lower than that of 46 underactive persons (2.14 ± 0.21 mg/100 ml.) ($P < 0.05$).

The relationships between symptoms, Venables activity scores, neuroleptic drug treatment, and magnesium levels in chronic schizophrenic men were next examined; the results are presented in Table 2. Pharmacotherapy lowered the magnesium concentration and increased the activity scores in every symptom group. So pronounced was the decrease in magnesium that only the smallest group of patients presenting solely with schizophrenic thought-disorder failed to display a significant difference. Patients manifesting secondary symptoms had significantly higher social and total activity scores after treatment. When the sub-groups were combined, significant increases in motor, social, and total activity scores matched the lowering in magnesium level. Analysis of variance yielded no significant interrelations between symptoms and magnesium level or between symptoms and activity scores.

When the frequency distributions of motor activity were plotted before or after medication, a definite bimodality with a trough at scores of 7 or 8 was

observed. This suggested that there were two distinct populations of schizophrenic patients: an underactive group scoring 7 or less out of 20, and an average group scoring 8 or more. The mean plasma-magnesium level in the untreated underactive group (2.35 ± 0.13 mg/100 ml.) was not significantly higher than that in the untreated group of average motor activity (2.24 ± 0.24 mg/100 ml.) comprising 50% of the total. However, the level in the treated underactive group (2.18 ± 0.16 mg/100 ml.) was significantly higher than that in the treated average group (2.07 ± 0.17 mg/100 ml.) ($P < 0.05$) comprising 60% of the total.

Correlation coefficients between pre- and post-treatment magnesium levels and age, period of hospitalization, and motor, social, and total activity scores on the Venables scale were then calculated. Only motor activity and magnesium concentration before drug therapy were significantly correlated ($r = -0.34$, $P < 0.05$). When the effects of age, length of stay in hospital, and social activity were allowed for, the partial correlation coefficient between magnesium level and motor activity became -0.40 ($P < 0.02$). The partial correlation coefficient between magnesium levels before and after treatment was 0.40 ($P < 0.02$) when the influence of motor and social activities was eliminated.

OTHER VARIABLES No significant correlations between magnesium concentrations and items on the scale of Harris *et al.* (1967) were found. Before and after treatment the mean concentrations in chronic male patients who smoked cigarettes did not differ significantly from those who were non-smokers.

PLASMA-MAGNESIUM LEVELS OF NON-SCHIZOPHRENIC PSYCHIATRIC PATIENTS To see whether the hypermagnesaemia of untreated chronic schizophrenic men was observed in institutionalized non-psychotic men, 40 patients were matched for age with 40 healthy men. The results of magnesium determinations and the effects of treatment are shown in Table 3. Those patients not receiving phenothiazine medication had significantly higher magnesium levels

TABLE 2

PLASMA-MAGNESIUM LEVELS AND ACTIVITY SCORES RELATED TO SYMPTOMS IN CHRONIC SCHIZOPHRENIC MEN

Symptom group	No.	Mean Mg $\pm$ SD (mg/100 ml.)			Mean motor activity $\pm$ SD			Mean social activity $\pm$ SD			Mean total activity $\pm$ SD		
		Untreated	Treated	P	Untreated	Treated	P	Untreated	Treated	P	Untreated	Treated	P
Thought-disorder	5	2.31 $\pm$ 0.14	2.12 $\pm$ 0.20	NS	7.0 $\pm$ 1.6	7.6 $\pm$ 1.8	NS	10.6 $\pm$ 3.0	13.4 $\pm$ 2.1	NS	17.6 $\pm$ 3.0	21.0 $\pm$ 2.9	NS
Cardinal	11	2.33 $\pm$ 0.18	2.09 $\pm$ 0.13	<0.001	6.7 $\pm$ 2.1	8.3 $\pm$ 1.7	NS	13.8 $\pm$ 3.8	15.8 $\pm$ 2.8	NS	20.6 $\pm$ 5.3	24.1 $\pm$ 3.5	NS
Secondary	16	2.29 $\pm$ 0.22	2.16 $\pm$ 0.17	<0.05	7.4 $\pm$ 1.8	7.7 $\pm$ 1.5	NS	11.8 $\pm$ 2.1	14.2 $\pm$ 2.0	<0.001	19.2 $\pm$ 3.4	21.8 $\pm$ 2.9	NS
Cardinal and secondary	8	2.24 $\pm$ 0.22	2.02 $\pm$ 0.18	<0.05	8.5 $\pm$ 2.3	9.3 $\pm$ 1.6	NS	13.8 $\pm$ 3.5	14.4 $\pm$ 2.3	NS	22.3 $\pm$ 5.4	23.6 $\pm$ 3.3	NS
Total	40	2.29 $\pm$ 0.20	2.11 $\pm$ 0.17	<0.001	7.4 $\pm$ 2.0	8.1 $\pm$ 1.7	<0.05	12.6 $\pm$ 3.2	14.6 $\pm$ 2.4	<0.001	20.0 $\pm$ 4.5	22.7 $\pm$ 3.3	<0.001

TABLE 3

EFFECTS OF TREATMENT ON PLASMA-MAGNESIUM LEVELS OF NON-SCHIZOPHRENIC MALE PSYCHIATRIC PATIENTS:
COMPARISON WITH NORMAL CONTROLS

Medication of patients	No.	Mean age $\pm$ SD (yr)		Mean Mg $\pm$ SD (mg/100 ml.)		P
		Patients	Controls	Patients	Controls	
On no drugs	19	56.6 $\pm$ 7.8	56.6 $\pm$ 8.1	2.33 $\pm$ 0.24*	2.14 $\pm$ 0.21	<0.01
On phenothiazines	13	49.5 $\pm$ 14.3	48.9 $\pm$ 13.9	2.16 $\pm$ 0.19*	2.06 $\pm$ 0.22	NS
On other drugs	8	51.8 $\pm$ 15.5	51.3 $\pm$ 16.4	2.31 $\pm$ 0.14	2.09 $\pm$ 0.16	<0.02
On any drugs	21	50.4 $\pm$ 14.4	49.8 $\pm$ 14.5	2.22 $\pm$ 0.18	2.07 $\pm$ 0.20	<0.02
Treated and untreated	40	53.4 $\pm$ 12.0	53.1 $\pm$ 12.3	2.27 $\pm$ 0.22	2.10 $\pm$ 0.20	<0.001

*These mean levels differ significantly ($P < 0.05$).

than did the controls. Those who were having phenothiazine medication did not have significantly higher levels. In addition magnesium levels were significantly lower in phenothiazine-treated men than in men not having any medication ($P < 0.05$). Comparison with the data of Table 2, which details findings with schizophrenic patients, indicates that magnesium levels of untreated schizophrenic and non-schizophrenic men did not differ significantly and levels of schizophrenic and non-schizophrenic men receiving phenothiazine derivatives also failed to differ significantly. As with the schizophrenic patients, smoking was without effect on the plasma-magnesium concentrations of non-schizophrenic males regardless of drug status.

DISCUSSION

Human plasma-magnesium levels appear to have no diurnal rhythm and are unaffected by normal eating habits and carbohydrate intake (Metz and Mours-Laroche, 1955; Stern and Lewis, 1960; Wallach, Cahill, Rogan, and Jones, 1962). That some effect of institutionalization is a relevant factor in this study is suggested by the finding that all but the phenothiazine-treated non-schizophrenics had high magnesium levels. Diet seems an unlikely cause of hypermagnesaemia in view of the experiment by Heaton and Parsons (1961). They supplemented a normal diet with magnesium salts to provide an increased intake of up to 500 mg per day but found no significant rise in the plasma levels of two males and two females, the increased absorption from the intestine being balanced by a similar increase in urinary excretion.

Institutional factors are likely to be only a partial explanation, since, among hospitalized patients, women had significantly higher levels of magnesium than did men. It is known that men fail to retain a magnesium load more readily than women under certain dietary conditions (Seelig, 1964). It is possible therefore, that an abnormality in magnesium metabolism exists in both sexes of schizophrenics

but, because of differential excretory ability, this does not become manifest as hypermagnesaemia in men.

Evidence on the influence of age is conflicting: Keating, Jones, Elveback, and Randall (1969) found no effect while Roberts (1967) described a positive correlation in women. Frank and Carr (1957) reported significant differences between serum concentrations at the menses and at the intermenstrual period. They also demonstrated an annual cycle. Neither of these rhythms is likely to have introduced a bias in the present study. Thus the chronic schizophrenic women, who displayed the most pronounced hypermagnesaemia, were of post-menopausal age. Further, as samples were collected from patients and healthy donors throughout the course of three years, an annual rhythm should not have produced any uncontrolled errors.

The present investigation throws some light on previously published results, some of which appeared contradictory. Thus while confirming the hypermagnesaemia reported by Cade (1964) in acutely-ill female patients, and supporting other observations (Katzenelbogen and Snyder, 1943; Brackenridge and McDonald, 1969), the normal values found by Seal and Eist (1967) in chronic schizophrenic men receiving phenothiazine drugs concur with our results. In the study of Masiak and Bernaskiewicz (1965) equal numbers of males and females were involved. In view of the sex differences in magnesium levels it is difficult to compare the present findings with the normal levels they encountered in early and chronic cases. The Polish workers found their chronic patients to possess significantly higher serum magnesium concentrations than subjects in an early phase before and after treatment. Again this is hard to corroborate for, while analysis of data in Table 1 shows the levels in chronic patients to exceed those in the acute patients, the values in their control subjects also differ significantly.

Considerable evidence for an association between activity and magnesium metabolism in schizophrenia has been presented in the present study but little

has been reported on their relationship in other conditions. The hypermagnesaemia observed in hypothyroidism (Wallach *et al.*, 1962) is associated with motor retardation. Conversely, Whang and Wagner (1966) found that exercise also caused an increased serum-magnesium level which was ascribed to an intracellular movement of water. It is unlikely that the hypermagnesaemia of schizophrenia arises by this mechanism because, at least in female geriatric patients (Brackenridge and McDonald, 1969), it is associated with a normal erythrocyte concentration of the metal. The increasing extent of withdrawal observed in patients passing from normality through acute to chronic psychotic phases is consistent with the corresponding increases in magnesium concentrations cited in Table 1. Whether this is cause or effect is unclear. The magnesium levels are more elevated in female patients than in males, and, because the increase persists when subjects are matched for age, it is not age-dependent. Chronic deteriorated schizophrenic women are not known to be generally more withdrawn than their male counterparts, so it is plausible that a sex-related factor is also operating.

It seems clear from the results in Tables 2 and 3 that neuroleptic drugs depress the plasma-magnesium level in both schizophrenic and non-schizophrenic patients; in the former an associated rise in activity occurs. Methylperidol and trifluoperazine were equally effective in decreasing magnesium concentrations in chronic schizophrenic men. In the non-psychotic group, from a variety of medication only neuroleptic drugs lowered the concentration significantly. Whether this is related to mode of action or is simply an epiphenomenon is uncertain.

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