Psychopharmacologia (Berl.) 44, 99–103 (1975) – © by Springer-Verlag 1975

The Effect of Lithium Treatment on Manic Symptoms and Levels of Monoamine Metabolites in Cerebrospinal Fluid of Manic Depressive Patients

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Received May 5, 1975

Abstract. Clinical effects, levels of 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA) in cerebrospinal fluid (CSF) and lithium levels in serum were examined in 13 manic depressive patients acutely admitted because of a manic or hypomanic episode. Patients were examined before and 12 days after the beginning of lithium treatment. Manic scores were significantly reduced during treatment. The levels of 5-HIAA as well as HVA increased significantly during treatment. The HVA to 5-HIAA ratio was significantly reduced, indicating a more pronounced change in 5-HIAA than in HVA. The 5-HIAA and HVA levels before as well as after 12 days of treatment were significantly correlated. No significant correlation was found between manic scores and monoamine metabolites in CSF or between lithium level in serum and reduction of manic scores or elevation of monoamine metabolites in CSF in the relative small number of patients studied.

Key words: Lithium – Manic Depressive Disorder – Cerebrospinal Fluid – 5-Hydroxyindoleacetic Acid – Homovanillic Acid.

There is now considerable evidence suggesting a role for the biogenic amines in the pathophysiology of manic depressive disorders (Schildkraut, 1965; Lapin and Oxenkrug, 1969; Sjöqvist, 1971; Sjöström and Roos, 1972; Åsberg *et al.*, 1973).

The results of studies on lithium effects on monoamine turnover in the brain of animals are controversial but in a number of studies lithium has consistently been found to increase the brain level of 5-hydroxyindoleacetic acid (5-HIAA), the deaminated metabolite of serotonin (Schildkraut *et al.*, 1969; Sheard and Aghajanian, 1970; Bliss and Ailion, 1970; Perez-Cruet *et al.*, 1971; Schubert, 1973).

The evidence for effects of lithium on monoamine turnover in the human brain is also ambiguous. Mendels (1971) reported that the level of 5-HIAA in the cerebrospinal fluid (CSF) increased during successful treatment with lithium in two manic patients. Similarly, Wilk *et al.* (1972) found a marked elevation of 5-HIAA in CSF of 2 manic patients in relation to lithium treatment. These observations are consistent with the results obtained in most animal experiments. However, an increase in 5-HIAA in CSF during treatment with lithium has not been observed in all clinical studies (Bowers *et al.*, 1969; Sjöström and Roos, 1972).

Wilk *et al.* (1972) reported a moderate elevation of homovanillic acid (HVA), the major dopamine metabolite, in CSF of their two manic patients during lithium treatment. Bowers *et al.* (1969) and Sjöström and Roos (1972), however, found no effect of lithium treatment on the level of HVA in the CSF of manic patients.

The apparent discrepancy in the literature may be due to the use of relatively insensitive fluorimetric techniques for metabolite determination and the small number of patients participating in the clinical studies. We therefore reinvestigated, in manic patients, the effect of lithium treatment on 5-HIAA and HVA levels in CSF using a highly sensitive and specific mass fragmentographic method. Relations between clinical effects, monoamine metabolites in CSF and lithium levels in serum were also analysed in the present study.

Methods

The study was performed on 13 patients acutely admitted to the clinic because of a manic or hypomanic episode. Five were men (age 18–69) and 8 were women (age 20–62). Prior to the manic episode all the patients had experienced one or more manic as well as depressive periods. None of the patients had any history or symptoms of organic brain damage, drug or alcohol abuse. The patients had not received any drugs for at least 1 month before the study. On admission and for the period up to the first lumbar puncture all patients exhibited symptoms of manic or hypomanic behaviour, characterized by flight of ideas, psychomotor and/or emotional

Table 1. Manic scores before and during lithium treatment

Pat. no.	Before treatment									After lithium treatment for 12 days								
	M	P	F	N	A	C	E	Σ	G	M	P	F	N	A	C	E	Σ	G
1	3	3.5	4	4	1	1	4	20.5	4	1	2	2.5	2	1	1	2.5	12	2.5
2	2	4	2.5	2	1	1	3	15.5	3	1	1.5	1.5	1	1	1	1	8	1.5
3	2	3	2	2	2	1	3	15	3	1	1	1	1	1	1	1	7	1
4	2	3	3	1	1	1	3	14	3	1	1	1	1	1	1	1	7	1
5	2	3	2	2	1	1	3	14	3	1	1	1	1	1	1	1	7	1
6	2	3	2	2	1	1	3	14	3	1	1	1	1	1	1	1	7	1
7	1.5	2	2	1.5	1	1	2	11	2	1	2	1	2	1	1	1	9	2
8	1	2	2	2	1	1	2	11	2	1	2	1	1	1	1	1	8	1
9	1.5	2	2	1	1	1	2	10.5	2	1	1	1	1	1	1	1	7	1
10	1	2	1	1	1	1	2	9	2	1	1	1	1	1	1	1	7	1
11	1	2	1	1	1	1	2	9	2	1	1	1	1	1	1	1	7	1

Data represent mean values for 2 independent raters.
M = Motor activity; P = Pressure of speech; F = Flight of ideas; N = Noisiness; A = Aggressiveness; C = Confusion; E = Elevated mood; G = Global rating.

excitement. The design of the investigation was approved by the Ethical Committee of the Karolinska Institute.

Administration of Lithium. Following a placebo period lasting from 1–4 days, treatment was initiated with a daily lithium dose of 48.6 mEq. Within the first week the dose was adjusted to 24.3–48.6 mEq to give a steady state concentration of lithium in serum (Sedvall *et al.*, 1970) within the therapeutic range of 0.7–1.4 mEq/l (Schou *et al.*, 1971). The placebo and lithium were administered four times daily and the tablets had a similar size, colour and composition of the inert ingredients. Each lithium tablet contained 0.3 g lithium carbonate (8.1 mEq lithium). No psychoactive drug in addition to the lithium and occasionally nitrazepam (Mogadon, Roche, 5 mg) for sleep induction were administered during the study.

Procedure for Rating of Mania. Rating of the clinical state of the patients was performed each time by the same two psychiatrists according to a scale for longitudinal rating of manic states (Petterson *et al.*, 1973). Eleven patients participated in the clinical evaluation and were rated for manic symptoms on the day before and 12 days after the beginning of lithium treatment.

Determination of 5-HIAA and HVA in CSF. Lumbar punctures were performed at 8 a.m. on the day before and on the 12th day following the start of the lithium treatment. The patients fasted for 12 hrs before the puncture, which was performed before the patient left his bed and before the first tablet of the day was administered.

A sample of 12 ml CSF was taken. After being mixed, the sample was divided into 2 ml portions and stored at − 20° C pending analysis. Storage of CSF samples for 4 months resulted in no significant diminution of the 5-HIAA or HVA levels. 5-HIAA and HVA were determined in duplicates within 2 months after the puncture. The CSF from the two punctures in each patient was analysed on the same day. The levels of 5-HIAA and HVA in CSF were determined simultaneously by the mass fragmentographic method described by Fri *et al.* (1974).

Determination of Lithium in Serum. Capillary blood samples for determination of lithium levels in serum were taken three times a week at 8 a.m. before the first tablet was administered. The lithium concentration was determined by atomic absorption spectrometry (Sedvall *et al.*, 1970). The lithium concentration in serum was below 0.05 mEq/l during the placebo period. After lithium treatment for 12 days it was 0.91 ± 0.07 mEq/l (mean ± S.E.).

Statistical calculations. Differences of means from paired and unpaired data and correlation coefficients were computed according to Pearson (1930) and Snedecor and Cochran (1967).

Results

The Effect of Lithium Treatment on the Clinical State. The interrater reliability for the different items of the rating scale used was high. The reliability coefficients at both the placebo and the lithium period were between 0.76 and 1.0 ($P < 0.05$ for all items).

The mean of the scores from the two rators before and after 12 days of lithium treatment is presented in Table 1. In all the patients there was a decline in the sum of scores during lithium treatment. The reduction in the sum of scores was highly significant ($P < 0.001$).

The Effect of Lithium Treatment on Levels of Monoamine Metabolites in CSF. The 5-HIAA and HVA levels obtained in double samples did not differ from each other by more than 10% in any case. This is in accordance with the previously reported high reproducibility of the method used (Fri *et al.*, 1974).

The mean levels of 5-HIAA and HVA and the HVA to 5-HIAA ratios before and during lithium treatment are presented in Table 2. No significant difference in the pretreatment values was found between men and women.

In all patients the 5-HIAA level in CSF was higher during the treatment than before (Fig. 1). The elevation

Table 2. Effect of lithium on 5-HIAA and HVA levels in CSF of manic depressive patients

	n	Age (years)	5-HIAA (pmole/ml)		*P*	HVA (pmole/ml)		*P*	HVA / 5-HIAA		*P*	Serum lithium level (mEq/l)
			Before lithium	During lithium		Before lithium	During lithium		Before lithium	During lithium		
Men	5	43 ± 9	103 ± 11	126 ± 6	< 0.05	212 ± 30	235 ± 27	> 0.05	2.12 ± 0.33	1.90 ± 0.26	> 0.05	0.97 ± 0.15
Women	8	48 ± 6	106 ± 15	152 ± 15	< 0.01	251 ± 37	336 ± 44	< 0.05	2.38 ± 0.24	2.18 ± 0.17	> 0.05	0.88 ± 0.07
Total	13	46 ± 5	105 ± 10	142 ± 10	< 0.001	236 ± 25	297 ± 31	< 0.05	2.28 ± 0.19	2.07 ± 0.14	< 0.05	0.91 ± 0.07

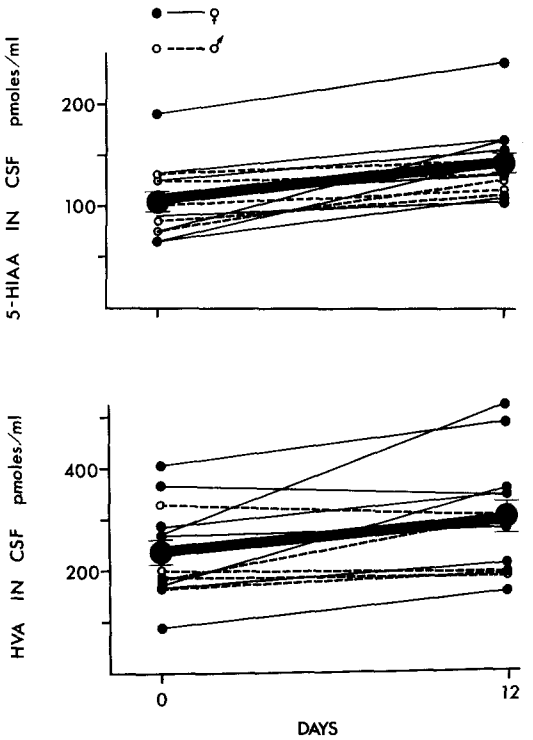

Fig. 1. The effect of lithium treatment for 12 days on levels of 5-HIAA and HVA in CSF of manic patients

was significant in men ($P < 0.05$), women ($P < 0.01$) and the whole material ($P < 0.001$) (Table 2).

In 10 out of the 13 patients, the HVA level in CSF was higher during than before lithium treatment (Fig. 1). When data from men and women were pooled a significant elevation was found ($P < 0.05$). Also in women ($P < 0.05$) a significant effect was observed (Table 2).

The HVA to 5-HIAA ratio was significantly reduced for the whole material as a result of the lithium treatment ($P < 0.05$) (Table 2).

Relations between 5-HIAA and HVA Levels. Significant correlations were found between the 5-HIAA and HVA levels before as well as after 12 days of lithium treatment ($r = 0.71$ and $r = 0.76$ resp., $P < 0.01$). The HVA to 5-HIAA ratio before treatment was also significantly correlated to the same ratio during treatment ($r = 0.90$, $P < 0.001$).

Relations between Manic Scores and Monoamine Metabolites in CSF. There was no significant correlation either before or during treatment between the sum of manic scores and the 5-HIAA or HVA levels or the HVA to 5-HIAA ratio. Neither was the difference in manic scores as a result of treatment significantly related to the elevation of the metabolite levels.

Relations between Pharmacokinetics and Pharmacodynamics of Lithium. There was no significant correlation between the lithium level in serum and the reduction of manic scores or the elevation of the monoamine metabolite levels in CSF.

Discussion

The present investigation aimed to study possible relations between psychopathology, central monoamine metabolism and pharmacokinetics in lithium treated manic depressive patients. Of the parameters analysed only the determination of lithium levels in serum represents a direct as well as accurate estimate. The quantification of the manic state by the type of rating scale used here has a high interrater reliability but the determination of its validity is met with several methodological difficulties. Determination of monoamine metabolites in CSF is accurate but indirect and represents the only practically available method for analysing monoamine metabolism in the CNS of psychiatric patients.

HVA in the lumbar CSF originates predominantly from dopamine metabolism in the brain (Post *et al.*, 1973a; Sourkes *et al.*, 1973). For 5-HIAA the problem is more complex. The presence of serotonin neurons in the spinal cord (Fuxe *et al.*, 1969) makes it likely that a substantial portion of the 5-HIAA in CSF is derived from such neurons. This view has been supported by studies in animals and man (Bulat and Zivkovic, 1971; Curzon *et al.*, 1971; Post *et al.*, 1973a). However, the finding that psychoactive drugs induce similar effects on 5-HIAA levels in human lumbar CSF as in the brain of animals, indicates that at least for pharmacological studies 5-HIAA levels in CSF reflect changes in CNS serotonin metabolism (Bowers, 1974; Bertilsson *et al.*, 1974).

In the present study all the manic patients were improved in relation to the lithium treatment. Simultaneously there was a significant elevation of the concentrations of 5-HIAA as well as HVA in CSF. The change in the 5-HIAA levels was more consistent than the change in HVA; it was also percentually greater. This is reflected by the significant diminution of the ratio between HVA and 5-HIAA during treatment. Thus it appears as if the change in 5-HIAA is more pronounced than the change in HVA, which is consistent with most findings in animal experiments and in the single patients studied by Mendels (1971) and Wilk *et al.* (1972).

Since the ratio between HVA and 5-HIAA was significantly altered it is unlikely that the elevation of acid metabolites was due to an effect of lithium on acid transport from the CNS. It is also unlikely that the elevation of the metabolite levels is due to a change in psychomotor activity. Post *et al.* (1973b) found that an increase in psychomotor activity elevated the HVA level more than the 5-HIAA level. We found a more marked effect on the 5-HIAA than on the HVA level, moreover the majority of patients became less anxious and active during treatment. Therefore a more likely interpretation of the present results is that lithium treatment causes an acceleration in serotonin, and possibly also dopamine, metabolism and turnover in the human brain. Bockar *et al.* (1975) reported that lithium therapy increased human platelet monoamine oxidase activity. If a similar effect is induced in the brain it may explain the present finding of an accumulation of the acid monoamine metabolites in CSF.

The effect of lithium on 5-HIAA in the manic patients is consistent with that obtained in experimental animals (Schildkraut *et al.*, 1969; Sheard and Aghajanian, 1970; Bliss and Ailion, 1970; Perez-Cruet *et al.*, 1971; Schubert, 1973). This makes it probable that the change in acid metabolites in CSF is an effect of the lithium ion rather than being secondary to the improvement of the patients.

There was no significant correlation between the reduction in manic scores and the change in the acid metabolite levels in CSF or the lithium concentration in serum. Neither were the changes in monoamine metabolites in CSF related to the lithium concentration in serum. These results do not preclude the possibility that such relations may be found in a larger patient material. Moreover, a greater variation, than in this study, in the serum lithium concentrations between patients, will give a better possibility to analyse relations between pharmacokinetics and pharmacodynamics of lithium.

Manic syndromes are generally considered to represent one aspect of manic depressive disorders. Controlled studies have shown unequivocally the therapeutic effects of lithium and tricyclic antidepressants on such states (Schou, 1968; Klerman and Cole, 1965). Antidepressant drugs like imipramine and amitriptylin block serotonin uptake in brain and reduce levels of 5-HIAA in the CNS of animals and man (Bruinvels, 1972; Bowers, 1974; Bertilsson *et al.*, 1974). The elevation of 5-HIAA levels in the CNS of animals and in the CSF of manic depressive patients found here may indicate that lithium primarily or secondarily affects transmission at serotonin synapses. Irrespective of the mechanism involved, the results are consistent with the view that brain serotonin, and possibly also dopamine, play a role in the mechanism of action of lithium. Tricyclic antidepressant drugs and lithium both normalize manic depressive states and alter serotonin metabolism in the brain, which

further implicates a role of this transmitter in the pathophysiology of manic depressive disorders.

Acknowledgements. The skilful assistance of Barbro Beck and Eva Rönnberg is gratefully acknowledged.

The investigation was supported by the Swedish Medical Research Council (21X-2291) and Karolinska Institutet.

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