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Serum Lithium Levels and Side Effects during Administration of Lithium Carbonate and two Slow Release Lithium Preparations to Human Volunteers

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Summary. Lithium carbonate, two slow release lithium preparations or placebo tablets were given to ten healthy volunteers for periods of eight days, and the lithium concentration in serum and subjective side effects were determined at various time intervals. A single blind randomized cross over design was used for the experiment. High peaks of the lithium concentration in serum occurred a few hours after administration of lithium carbonate. Slow release preparations produced more constant lithium concentrations in most subjects. — Subjective symptoms were more common after lithium preparations than after the placebo. Symptoms like nausea and general fatigue seemed to increase in frequency during the treatment periods and to be related to a high lithium level in serum. Tremor occurred in only two subjects with low serum lithium concentrations and, usually appeared from the first day of administration. One of the slow release preparations, which contained lithium sulfate, caused a high frequency of diarrhoea, which was presumably due to the release of lithium or sulfate ions in a lower part of the gastrointestinal tract.

Two decades have passed since Cade (1949) introduced lithium salts for treatment of manic episodes. The therapeutic effect of lithium in this disorder is now well documented (see Schou, 1968). Lithium carbonate is the salt most often used. Due to its rapid absorption, the concentration of lithium in serum varies considerably during the day, with sharp peaks during the first few hours after administration (Amdisen, 1967; Amdisen and Schou, 1967; Jönsson and Sedvall, 1967). Lithium treatment is often accompanied by side effects, some of which have been reported to appear within the first few hours after ingestion of the tablets and to coincide with the peak of lithium concentration in serum (Amdisen and Schou, 1967; Jönsson and Sedvall, 1967). Lithium has usually been administered in three or four daily doses to keep the serum level as constant as possible. In order to prolong the interval between doses various types of slow release lithium preparation have recently been developed (Amdisen and Sjögren, 1968; Coppen *et al.*, 1969).

The aim of the present study was to investigate whether slow release preparations of lithium salts offer advantages as regards constancy of serum levels and frequency of side effects. An attempt was also made to relate the occurrence of side effects to serum levels of lithium. Unfortunately one of the slow release preparations could only be obtained with a lower lithium content than the other preparations. Therefore the frequency of side effects for this preparation can not directly be compared with those of the other preparations.

Methods

The study was performed on ten physically and mentally healthy human volunteers, 17—34 years of age. Four were males, six females. None of the individuals used any other drug than lithium during the study. No restrictions with regard to diet or fluid intake were demanded.

Subjects were told to note carefully in their own words the type and time course of all subjective symptoms experienced during the day. This record of side effects was obtained from each subject at the end of the day.

Lithium was administered in three different tablet preparations:

1. Lithium carbonate, containing 8 mEq of lithium per tablet.
2. "Lithium durules", containing 6 mEq of lithium as sulfate in an insoluble plastic matrix (Lithionit Duretter®, AB Hässle, Sweden).
3. "Lithium lipetts", containing 8 mEq of lithium as sulfate dissolved in fat (Litium Lipetter, ACO Läkemedel, Sweden). This preparation was made specially for this study and has since then been developped further.

Three different placebo tablets were used, each similar to one of the three lithium preparations as regards size, colour and composition of the inert ingredients.

All six different preparations were administered to each subject in random order, using a single blind cross over design. Each period of lithium was followed by a period of placebo administration. Tablets were taken three times daily, one at 8 a.m., one at 12 and two at 4 p.m. The subjects received each lithium preparation for 8 days, and between the lithium periods a placebo was given for the same length of time. During the first and the eighth day of each administration period, blood samples for determination of lithium in serum were taken from the finger tip at various time intervals (see Figs. 1—6). During the intervening periods

blood samples were collected every day at 8 a.m., before administration of the first tablet.

For determination of the lithium concentration, 25 µl of serum was dissolved in 1 ml of 0.4 N perchloric acid, and the protein precipitate removed by centrifugation. The lithium concentration was determined by atomic absorption spectrometry. In model experiments a linear relation between absorbance and amount of lithium added to serum up to 3.0 mEq/l was found. Concentrations of sodium, potassium and calcium within the physiological range found in serum, did not interfere with the determination of lithium by this method. The lithium concentration in fingertip blood did not differ significantly from that of blood taken simultaneously from the antecubital vein. The experimental error (S.D.) of the method, determined from ten double samples, was less than 2%.

Results

Lithium concentration in serum

The mean lithium concentrations in sera from subjects during the first day of administration of lithium carbonate, lithium durules and lithium lipetts

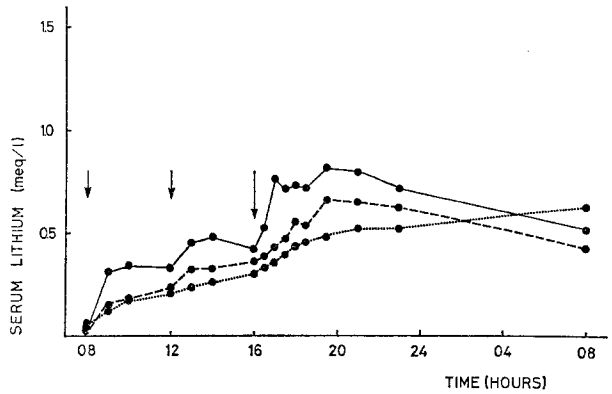

Fig. 1. Mean lithium concentration in serum of 10 subjects during the first day of administration of lithium carbonate (———), lithium durules (— — —) and lithium lipetts (. . . . .). Arrows indicate tablet administration; the doses of lithium were 8+8+16 mEq for carbonate and lipetts and 6+6+12 mEq for the durules. Each point represents the mean value from 7 to 10 subjects. For further details see text

is presented in Fig. 1. During administration of lithium carbonate a peak in serum concentration was obtained about two hours after each dose, whereas the concentration rose more evenly with the two slow release preparations. Following administration of the durules the concentration was highest about four hours after administration, whereas the mean lithium concentration after the lipetts still seemed to be increasing sixteen hours after administration of the last tablet.

Large individual differences were found. In some subjects the concentration rose evenly following all three preparations (Fig. 2). In other individuals very high peaks were obtained after lithium carbonate, whereas no peaks at all were present after the two slow release preparations (Fig. 3).

The mean lithium concentrations in sera of the subjects during the eighth day of administration is presented in Fig. 4. Distinct peaks were obtained 1 to 2 h after administration of lithium carbonate. Following the durules peak values were lower and occurred 2 to 3 h after administration. At all time intervals the lithium concentration in serum was lower than during administration of lithium carbonate. (The daily dose of lithium during durule administration was lower than during administration of the other two preparations.) The lipetts gave a very constant concentration of lithium over the day. Morning values were about the same as after lithium carbonate.

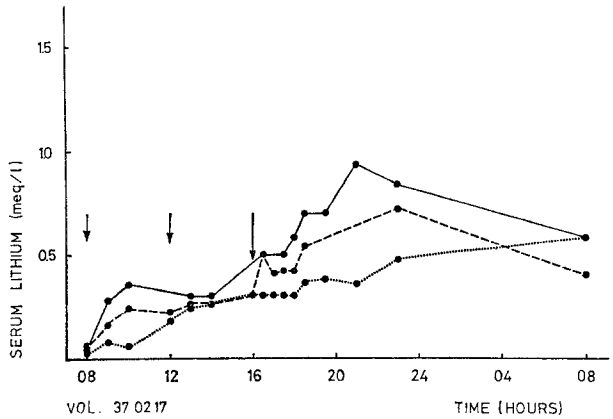

Fig. 2. Lithium serum concentration of subject 37 02 17 during the first day of administration of lithium carbonate (———), lithium durules (— — —), lithium lipetts (. . . . .). Arrows indicate tablet administration. For further details see text

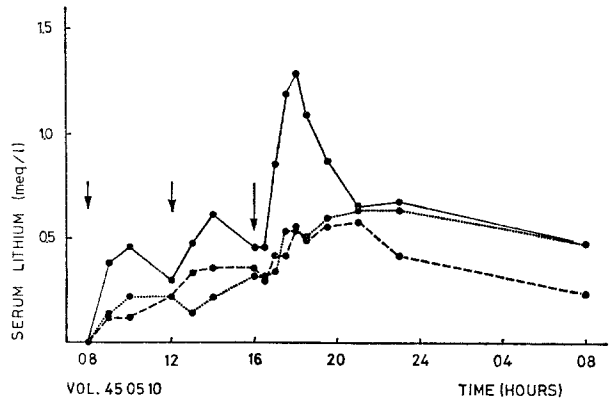

Fig. 3. Lithium serum concentration of subject 45 05 10 during the first day of administration of lithium carbonate (———), lithium durules (— — —) and lithium lipetts (. . . . .). Arrows indicate tablet administration. For further details see text

The relative heights of the peak values for lithium concentration in serum after treatment with the various preparations were calculated by expressing the maximal lithium concentration for each subject on the eighth day of treatment as percentages of the morning value on the same day (Table 2). It was found that

the relative peak height was significantly higher after lithium carbonate than after the slow release preparations. Lithium lipetts gave significantly less variation in the serum lithium levels during the day than did the lithium durules.

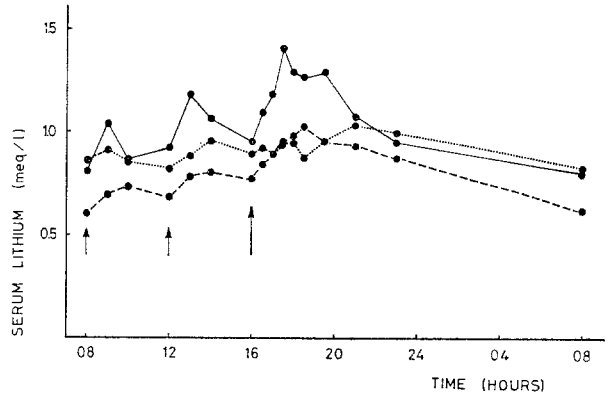

Fig. 4. Mean lithium concentration in serum of 10 subjects during the eighth day of administration of lithium carbonate (———), lithium durules (— — —) and lithium lipetts (.....). Arrows indicate tablet administration; the doses of lithium were 8+8+16 mEq for carbonate and lipetts and 6+6+12 mEq for the durules. Each point represents the mean value for 7 to 10 subjects. For further details see text

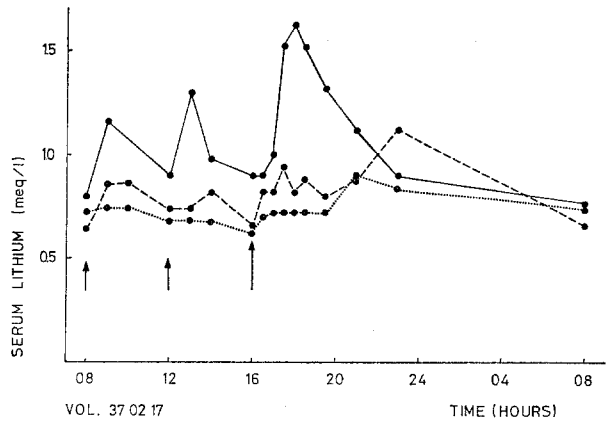

Fig. 5. Lithium serum concentration of subject 37 02 17 during the eighth day of administration of lithium carbonate (———), lithium durules (— — —) and lithium lipetts (.....). Arrows indicate tablet administration. For further details see text

During the eighth day of administration there were large individual variations in the heights of the peak concentrations, e.g. the subject presented in Fig. 5 exhibited very high peaks following administration of lithium carbonate but practically no peaks following the two slow release preparations. On the other hand, the subject presented in Fig. 6 had a marked variation in serum lithium concentration also after administration of the slow release preparations.

The half life of lithium in serum was found to be about 24 h for all preparations (unpublished data), and after 4 days of placebo administration the lithium concentration in all cases was less than 0.1 mEq/l.

Occurrence of subjective symptoms

The number of subjects experiencing side effects of various kinds, and the number of days on which these effects occurred are presented in Table 1. The frequency of side effects was higher during lithium carbonate treatment than during placebo administration, in terms of both the number of subjects and total number of days concerned.

The most common side effects were general fatigue, nausea, diarrhoea and tremor. These side effects, except the tremor, were most frequent during the latter part of the treatment period, but the tremor occurred throughout this period. In most cases nausea and vomiting appeared a few hours after the intake of the two tablets in the afternoon, whereas the other symptoms were present throughout the day.

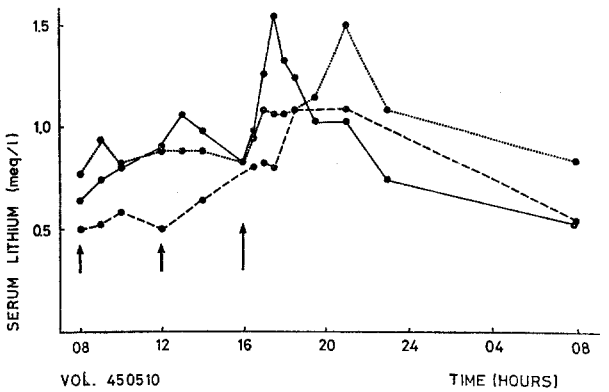

Fig. 6. Lithium serum concentration of subject 45 05 10 during the eighth day of administration of lithium carbonate (———), lithium durules (— — —) and lithium lipetts (.....). Arrows indicate tablet administration. For further details see text

Side effects also occurred during placebo administration, but here they were most common during the first days of the treatment periods when the lithium concentration was still declining following the previous period of lithium administration.

During periods of lithium durule administration the frequency of side effects was lower than during treatment with lithium carbonate, and this must be due, at least in part, to the smaller amount of lithium given during these periods. During lipett administration side effects were similar to those of lithium carbonate, except for a greater frequency of diarrhoea which occurred throughout the treatment and which lasted all day. The frequency of nausea and general fatigue seemed to be lower than during lithium carbonate administration.

Discussion

In the present study serum levels of lithium and subjective side effects were studied in a group of human volunteers during the administration of lithium car-

bonate and two slow release preparations containing lithium sulfate.

Amdisen and Sjögren (1968) compared lithium carbonate and lithium durules containing lithium sulfate in a few subjects. Their results indicated that the slow release preparation produced less variation in serum lithium level than did lithium carbonate. In the present study, both the types of slow release preparation were found to produce significantly less variation in serum lithium concentration than lithium carbonate (Table 2). During administration of the slow release preparations the highest value during the day appeared later and was considerably lower than after administration of lithium carbonate and lithium lipetts was 32 mEq, and during periods of durule administration 24 mEq of lithium. This explains why on the eighth day of administration the serum lithium concentrations were lowest for the durules.

No controlled study of side effects following lithium administration appears to have been published before the present one. However, clinical observations indicate that tremor, nausea and muscular weakness are side effects which also occur at low serum levels (Schou, Amdisen and Trap-Jensen, 1967). The analysis of side effects reported by the subjects in the present study clearly indicates that the active ingredients of the pre-

Table 1. *Subjective symptoms during administration of lithium carbonate (C), lithium durules (D), lithium lipetts (L) and placebo preparations. The daily dose of lithium was 32 mEq in the carbonate tablets and lipetts, and 24 mE in the durules. Figures indicate the number of individuals affected and the number of days on which symptoms appeared*

Symptom	Individuals						Days											
	Lithium			Placebo			Lithium						Placebo					
	C	D	L	C	D	L	C		D		L		C		D		L	
							Day: 1–4	5–8	1–4	5–8	1–4	5–8	Day: 1–4	5–8	1–4	5–8	1–4	5–8
Thirst	1	2	1	—	—	—	4	4	5	6	4	4	—	—	—	—	—	—
Nausea	6	1	3	1	—	—	1	7	—	2	5	8	4	1	—	—	—	—
Vomiting	—	—	1	—	—	—	—	—	—	—	2	—	—	—	—	—	—	—
Diarrhoea	3	1	7	3	1	2	—	5	1	—	16	15	6	1	2	—	3	1
Tremor	2	3	4	—	—	—	8	8	9	8	15	16	—	—	—	—	—	—
General muscle weakness	1	1	—	—	—	—	—	1	—	2	—	—	—	—	—	—	—	—
Headache	1	1	2	1	1	—	2	1	1	—	4	4	1	—	3	—	—	—
General fatigue	7	4	4	4	3	2	9	16	9	8	4	8	13	4	7	—	2	2
Total	21	13	22	9	5	4	24	42	25	26	50	55	24	6	12	—	5	3

Table 2. *Maximum values of the serum lithium concentrations on the eighth day as per cent of the morning value on that day*

Lithium carbonate	$209^a \pm 11$
Lithium durules	$184^b \pm 5$
Lithium lipetts	$136^c \pm 8$
$a>b$	$p<0.02$
$a>c$	$p<0.001$
$b>c$	$p<0.001$

The data represent mean ± S.E.M. of 10 subjects

lithium carbonate. However, in a few subjects, the peak values were as high as after carbonate (Fig. 6), indicating that these slow release preparations do not always produce a constant lithium concentration in all subjects. Such variations could be due to individual differences in gastrointestinal function. Therefore, these slow release preparations should be administered with caution, and it might be of value to determine the serum lithium concentration twice daily during the initial period of administration, i.e. in the morning, and a few hours after the last daily dose when the lithium level is highest.

In the present study all subjects were given four tablets a day, which means that the daily dose during parations, i.e. lithium carbonate and lithium sulfate, produce effects that can be recorded subjectively. Thus, the frequency of reported side effects was much lower during placebo administration than during treatment with active preparations. Moreover, side effects during placebo periods appeared at the beginning of treatment, suggesting that they were due, in part at least, to lithium remaining in the tissues (Table 1). Significant amounts of lithium were still present in serum during the first four days of placebo administration.

One of the aims of the present study was to determine the types of side effects which occur during lithium therapy, and for this reason subjects were not informed of the symptoms expected. This approach and the use of only a small number of subjects does not permit quantitative correlation of side effects with lithium levels in serum. However, the study allows us to draw some tentative conclusions about the time course of appearance of side effects and their relationship to lithium concentration in the serum.

General fatigue, nausea, diarrhoea and tremor were the most common side effects during lithium carbonate administration. The incidence of nausea increased towards the end of the treatment period, and appeared

in most cases within a few hours after the last dose of the day. Since the serum lithium concentration rose constantly throughout the administration period, and reached its maximum level a few hours after the intake, there seems to be a relation between lithium concentration in serum and the incidence of nausea. A similar relation might also exist for the feeling of "general fatigue", and diarrhoea. Two subjects reported tremor throughout the period of treatment with lithium carbonate, and, unexpectedly, these subjects had lower lithium levels than any of the other subjects, indicating considerable differences in individual sensitivity to lithium, or of ability to perceive tremor.

The most pronounced side effect was diarrhoea during the period of lipett administration. This diarrhoea appeared at the beginning of the period of treatment and lasted throughout the day, implying that it was not related to the lithium concentration in serum. The frequency of diarrhoea during the lipett placebo period was low, suggesting that the lipett matrix was not the causative factor. The lipetts contained lithium sulfate. Since lithium carbonate did not give a high frequency of diarrhoea the sulfate ion in the lipetts might be responsible for this symptom. The frequency of diarrhoea was low following administration of durules that also contained lithium sulfate, but in the latter preparation, the amount of lithium sulfate was lower which might account for the observed difference. An alternative explanation for the diarrhoea during lipett administration might be that the lithium in the lipetts is released in a lower part of the gastrointestinal tract than the lithium in the other two preparations. The very constant lithium concentration in serum during lipett administration supports this view.

Other side effects such as thirst, nausea, tremor and general fatigue seemed to occur at about the same frequency after the use of either slow release preparations or lithium carbonate, when allowance is made for the lower content of lithium in the durules.

For a prophylactic effect against manic-depressive relapses, the concentration of lithium in serum should be 0.8 to 1.2 mEq/l in the morning according to Schou *et al.* (1970). In this study the mean lithium concentration of the subjects in the morning on the eighth day of durule administration was less than 0.6 mEq/l. This means that more than the 24 mEq of lithium per day, used in the present study, should be given to most patients in order to achieve an optimum concentration in serum.

The subjective symptoms reported here represent the acute effects of lithium in human volunteers. It seems likely that during long term administration, patients develop tolerance towards these effects (Schou *et al.*, 1970). Thus, the relatively high frequency of side effects reported in the present study should be redarded as maximal. Most subjects in the study considered that the side effects of the administration of active preparations were incapacitating, in spite of the relatively low serum lithium concentrations achieved. It seems necessary therefore to inform patients about the side effects which may occur during the initial period of treatment.

It is well known that lithium has a narrow therapeutic range and that serious intoxication may occur. The present study indicates that lithium concentrations in the lower therapeutic range may also cause acute effects that do not seem to be any less incapacitating than those produced by most other psychoactive agents.

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