

## BRIEF COMMUNICATION

### Monitoring of lithium therapy

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#### **Abstract:**

Results of serum lithium performed in the Chemical Pathology Laboratory, Universiti Kebangsaan Malaysia, Kuala Lumpur, over a years' period (June 1991 till May 1992) formed the subject of study. A total of 277 tests were carried out on 148 patients, giving a frequency of about 23.1 tests per month. Complete data regarding age, sex and ethnic group was available for 140 subjects. There were 74 males and 66 females. Racial distribution was 72 Malays, 42 Chinese and 26 Indians. Their ages ranged from 15 to 80 years. One hundred and twenty-three subjects (87.6%) were within the 3rd to 5th decade of life. 136/277 (49.1%) of serum lithium levels were less than 0.6 mmol/l and 24/277 (8.7%) gave results greater than 1.0 mmol/l. Only 6 tests gave values which exceeded 2 mmol/l. This study reveals the need to conduct a prospective study to determine the underlying cause of the high incidence of low serum lithium levels and whether this situation is associated with a satisfactory treatment response in the said population.

**Key words:** Lithium, therapy, population studies, therapeutic range.

#### **INTRODUCTION**

The role of therapeutic drug monitoring is well-established for some drugs. The indications for measuring serum drug levels are (1) monitoring drugs for their therapeutic response, namely to check on compliance and adequacy of the dose achieved, (2) diagnosis of obscure conditions and (3) elucidation of the drug taken in overdose. It is necessary to monitor lithium therapy because of its narrow therapeutic index and the likelihood of non-compliance by psychiatric patients. Lithium measurement has become one of the clinically useful test in the armamentarium of biochemical tests. However, to appreciate its effect fully, it is essential to use the drug correctly.

Lithium is an alkali ion in group IA sharing many properties with other elements in this group such as sodium and potassium, as well as some properties of ions in the 2A group such as calcium and magnesium.<sup>1</sup> Rapid absorption takes place in the gastrointestinal tract with peak blood levels occurring approximately 1-3h after oral ingestion and is completed in approximately 8 hrs. It is not protein-bound and serum steady state is usually achieved 4 to 6 days on a fixed dose. When measuring the serum level of lithium, blood should be taken about 12 hours after the last dose. Excretion is almost entirely through the kidneys.

It is important to note that proximal reabsorption of sodium and lithium in the kidneys is similar. Increased retention of lithium may be

precipitated by states of sodium depletion, hence raising the potential for toxicity. This leads to a very narrow margin of safety for lithium and requires careful instruction to the patient regarding changes in diet, exercise pattern or use of medications that may in some way significantly alter the ingestion or excretion of sodium. Finally, significant drug interactions may occur with lithium and several anti-inflammatory agents (e.g. indomethacin, phenylbutazone and ibuprofen) leading to decreased lithium clearance and increase in serum level. This may necessitate a lowering of dosage to prevent toxicity.'

Lithium is the drug of choice in the treatment of hypomania and acute mania, as well as in the prophylaxis of recurrent bipolar illness. The first successful trial in manic patients was demonstrated by Cade<sup>2</sup> in 1949 and Schou's<sup>3</sup> double-blind controlled trial illustrated lithium's clear superiority over placebo. Despite the drug's clinically proven efficacy, lithium has a narrow therapeutic window (0.6 to 1.0 mmol/l) and can lead to serious neurological, endocrinological, cardiac and renal toxicities.

Therefore, lithium is one of the drugs which needs constant monitoring in order to ensure effectiveness of treatment. In our laboratory, the therapeutic range is taken as 0.6 to 1.0 mmol/l. Below the range, lithium may not be effective, whereas values of greater than the range may give rise to toxicities. Dosages may have to be

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individualised in order to gain full benefit of lithium therapy.

The object of this study is to investigate the pattern and outcome of lithium requesting.

**MATERIALS AND METHODS**

Data of lithium tests performed in the chemical pathology laboratory, Department of Pathology, University Kebangsaan Malaysia over a period of about a year (June 1991 till May 1992) were retrieved from the computer. Lithium was analysed using atomic absorption spectrophotometry. A profile of the population being investigated in terms of age, sex and racial distribution as well as the frequency of testing and the serum lithium levels achieved in the patients, were obtained. This being a retrospective study, there was no attempt to correlate serum lithium levels with the patients' clinical status.

**RESULTS**

The test population comprised 72 Malays (51%), 42 Chinese (30%) and 26 Indians (19%). This may reflect the distribution of the patient population attending the clinics in Kuala Lumpur Hospital, rather than a racial propensity to the illnesses necessitating lithium treatment. There were 74 males and 66 females.

Table I shows the distribution of the test population according to age, race and sex. One hundred and twenty-three patients (87.6%) were in the 3rd to 5th decade of life.

Fig. 1 shows the distribution of serum lithium levels in the test population. More than half of the subjects (57.8%) achieved levels outside the reference therapeutic range with 49.1% showing values lower than 0.6mmol/l.

**TABLE 1: Distribution of population on lithium therapy according to age, race and sex**

Age-group (yr)	Malay		Chinese		Indian		Total
	M	F	M	F	M	F	
11-20	4	2	1	2	0	0	9
21-30	14	9	5	5	3	6	42
31-40	12	7	8	10	3	4	44
41-50	11	9	6	4	3	4	37
51-60	0	2	0	0	0	2	4
61-70	2	0	0	0	1	0	3
71-80	0	0	1	0	0	0	1
Total	43	29	21	21	10	16	140

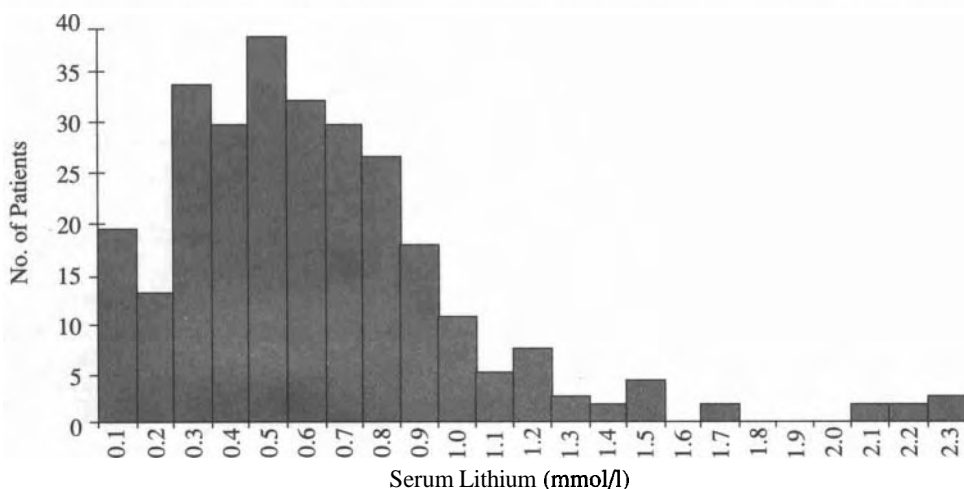


FIG. 1: Distribution of serum lithium levels from the test population

## DISCUSSION

Janicak<sup>1</sup> in his discussion on treatment issues with lithium recommended that the usual starting doses are 600-1200mg/day. Lithium's half-life is approximately 24h and it takes about 4-5 half-lives to achieve steady state blood levels. Therefore, the initial and subsequent blood levels should be drawn every 4 to 6 days, thus allowing steady state serum levels to be achieved before a decision to adjust the lithium dose is made. The standard time for blood levels to be drawn is 10 to 12hr after the last dose of lithium. If not adhered to, the levels will not be as useful in assessing the need for dosage alteration.

The range of therapeutic treatment dose can vary from 300-3000mg of lithium per day with the average falling between 900 - 1800mg/day. However age, renal function and general physical conditions are important associated determining factors for the ideal dose. The therapeutic serum level is quoted as between 0.5 - 1.5mmol/l, but this must be balanced by one's clinical observation of response and side effects or toxic profile in a given patient. Although, many clinicians may try to achieve the serum lithium within the widely accepted therapeutic range, it is not inconceivable that many patients may not tolerate the typical therapeutic levels and can be managed successfully at a lower level without signs of toxicity.

The high percentage of tests with low serum lithium (49.1%) in this study bring to question whether (1) a majority of patients may not be complying with their medication regime, (2) the blood levels were not taken at the correct time (i.e. 10-12 h after the last dose), (3) the majority of patients were being well-maintained and stabilised at a much lower serum lithium levels than normally accepted in the literature or (4) a combination of all the factors described should be considered. It is tempting to consider that the observations reflect the possibility that Malaysians overall exhibit a lower tolerance to lithium therapy. However, further studies are required to support this view.

In summary, this retrospective study of serum lithium measurements in a Malaysian population has shown a preponderance of serum lithium levels lower than the accepted therapeutic range. A prospective study is required to determine the cause of this finding, so that appropriate recommendations can be made.

## ACKNOWLEDGEMENTS

The authors wish to thank the staff of the Chemical Pathology Laboratory, Universiti Kebangsaan Malaysia for their dedicated involvement in the

analysis of serum lithium during the period of study.

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