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LITHIUM THERAPEUTIC DOSE MONITORING IN HUMAN SALIVA

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SUMMARY

Background: *Lithium carbonate is valuable and effective agent in the treatment and prophylaxis of mood disorders, particularly bipolar disorder (BD). Due to its narrow therapeutic range, frequent serum lithium estimation is necessary. To avoid the discomfort of frequent venipuncture, a non-invasive method for serum lithium concentration is needed. An alternative method of determining lithium level could be saliva or urine. Literature data regarding the reliability of saliva lithium levels is not conclusive.*

Material and methods: *The aim of this study is to provide an overview of possibility to replace blood serum with saliva look through research in that field.*

Results: *Some authors conclude that there is constant ratio between serum and saliva lithium level and they suggest that saliva can replace serum for estimation lithium level. Other revealed that saliva/serum lithium ratio is constant individually, so saliva/serum lithium ratio should be estimated individually. Finally there are studies excluding the possibility of replacement serum with saliva.*

Conclusions: *There is little number of studies on saliva clinical use in lithium level monitoring. Further studies should base on current data including methods of obtaining saliva and its biochemical analysis, collecting samples in a specific time frame from the last dosage of lithium, as well as inter-subject or intra-subject measurements.*

Key words: *monitored therapy - lithium carbonate - bipolar disorder - saliva*

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INTRODUCTION

Lithium carbonate is an effective agent widely used in the treatment and prophylaxis of mood disorders, particularly bipolar disorder (BD) (Aubry 2007, Grandjean 2009a, Grandejan 2009b). It is also used in augmentation therapy for severe, refractory depression, and suicide prevention (Cipriani 2013, Focosi 2009, Rybakowski 1999). Due to its narrow therapeutic range, frequent serum lithium estimation is necessary (Mitchell 2000, Hopkins 2000). In BD prophylaxis, the monitoring of lithium concentrations is recommended every 3 – 6 months (Ng 2009). The measurement should be performed 8-10 hours after the last dosage of the drug and after at least 5 half-lives duration (Granedjean 2009). To avoid the discomfort of frequent venipuncture, a non-invasive method for serum lithium concentration is needed. An alternative method of determining lithium level could be saliva or urine (Langan 2007, Nunes 2015). Literature data regarding the reliability of saliva lithium levels is not conclusive.

The aim of this study is to provide an overview of possibility to replace blood serum with saliva look through research in that field.

RESULTS

In recent years use of biological materials to substitute of serum for estimation of lithium concentration has been studied. On reviewing literature on this subject, there was no statistical significancy between serum and urine lithium concentration (Tadeusiak 1992; Shetty 2012). Several studies revealed higher lithium concentration in saliva than in serum. Lithium concentration index saliva/serum was stable for at least 3 months despite of variable serum lithium concentrations (Groth 1974; Lazarus 1973). Nataraj and Bhat (1981) revealed that the lithium concentration saliva/serum index was constant for individual and after some time suddenly changed. There was no clear explanation for this phenomenon.

Neu at al. (1975) proved that the metabolic phase of lithium had no effect on intraindividual measurements. Serdarevic et al. (2006) observed that higher correlation of lithium concentrations in saliva and serum was found after 2 hours of receiving the drug. The time since the last dosage of the drug and the time of the entire lithium therapy also did not matter (Bowden 1982). Ben-Ayreh et al. (1984) conducted study with 22 patients diagnosed BD on lithium therapy and a 21 controls. The results showed a significant correlation between saliva and serum lithium concentration which suggest the possibility of clinical saliva use in lithium concentrations estimates during therapy. Khare et al. (1983) in a group of 60 BD patients on lithium therapy, revealed that the ratio of salivary/serum levels to that of serum was from 1.77 to 6.68 with 51% of the samples was between 3 and 3.99. The result suggest that it is important to identify the subgroup of patients with better correlation of salivary and serum lithium concentration and also determine each individuals ratio to monitor that particular individual therapy (Table 1).

Several studies revealed variation in ratio saliva/serum lithium concentration in both inter-individual and intra-individual (Mc Kage 1989; Moody 1999; Nataraj 1981; Obach 1988).

Table 1. Saliva use in therapeutic lithium concentrations monitoring

Author, year	Number of patients	Diagnosis	Lenght of lithium intake	Metabolic phase	Concomitant treatment	Stimulated saliva
Nataraj & Bhat 1981	28	Different diagnosis	2 weeks	12 h since last llithium dose	No data	Yes
Bowden et al. 1982	40	Different diagnosis	chronic	10-13 h since last llithium dose	Yes	Yes
Khare et al.1983	60	Bipolar disorder	1-6 years	12 h since last llithium dose	Yes	Yes
Ben-Aryeh et al. 1984	22	Bipolar disorder and healthy control	5 years	12 h since last llithium dose	No	No
Obach et al. 1988	8	Healthy control	One lithium dose	30 minutes after lithium dose	No	Yes
McKeage & Maling 1989	28	No data	No data	12-16h since last llithium dose	Yes	No data
Tadeusiak et al. 1992	31	No data	At least one year	No data	No data	Some saliva samples stimulated other unstimulated
Moody 1999	9	Bipolar disorder	No data	No data	Yes	No
El-Mallakh et al. 2004	11	Bipolar disorder	At least 3 months	8-12h since last llithium dose	No data	No
Serdarevic et al. 2006	25	No data No	4 months – 13 years	2h and 12 h since last llithium dose	No data	No
Shetty et al. 2012	50	No data	At least 1 week	12h since last llithium dose	Yes	No

Author, year	Information about xerostomy, fasting status, oral infections etc.	Separation of muccopolysaccharide and water saliva fraction	Inter/intra-subject differencies	Possible replacement serum to saliva
Nataraj & Bhat 1981	No data	Yes (centrifugation)	Yes	No
Bowden et al. 1982	No data	Yes (centrifugation and dilution)	Yes	Yes (intrasubject)
Khare et al.1983	Yes	No data	Yes	Yes (intrasubject)
Ben-Aryeh et al. 1984	Yes	Yes (centrifugation)	Yes	Yes
Obach et al. 1988	Yes	Yes (centrifugation)	Yes	No
McKeage & Maling 1989	No data	No	Yes	No
Tadeusiak et al. 1992	No data	Yes (centrifugation)	No data	Yes
Moody 1999	No data	No	Yes	No
El-Mallakh et al. 2004	No data	Yes (centrifugation and dialysis)	No data	No
Serdarevic et al. 2006	No data	No	Yes	Yes
Shetty et al. 2012	Yes	No	Yes	No

Due to the discrepancies regarding the effectiveness of using saliva for lithium monitored therapy, another issue was analyzed in relation to methods of obtaining and processing saliva. Saliva consists of water and the mucopolysaccharide parts. Lithium is stored mainly in the water part. Centrifugation or dialysis of saliva improves the quality of lithium measurements. El Mallakah et al. (2004) analyzed impact of saliva dialysis on lithium level measurements indicating the lithium concentrations in dialised saliva in comparison with

serum were converged but still the data was insufficient to replace serum with saliva. However, the study had some limitations with small number of patients (10 subjects), conditions of saliva samplings (patients were not fasting, measurements were conducted during different hours) and of storage conditions which could not allow to the highest reproducibility of the results.

Saliva, as a biological material, requires specific sample collecting methods. It is confirmed that unstimulated saliva is a better material for analysis (Chiapin 2007). Literature data suggests that saliva secretion was often stimulated (e.g. chewing) and this might have affected sample quality. Tadeusiak et al. (1992) used Salivette sampling device which allowed unstimulated saliva collection. Results showed significant correlation between lithium concentrations in serum and saliva what allowed to conclude that serum could be replaced with saliva. However, other studies did not confirm those results (Shetty 2012).

DISCUSSION

Literature data revealed higher concentration of lithium in saliva than in serum. This can be explained by the fact that lithium ions are eliminated slower from saliva than from serum as well as by the active transport to saliva (Langman 2007, Serdarevic 2006). The finding is of clinical importance. However, several considerations must be taken into account in saliva sampled for lithium determination in monitored therapy. In particular, the collection process must be corrected with regard to xerostomia, tobacco smoking, mouth illnesses, brushing of teeth and fasting status. Saliva was often diluted leading to a decreased quality of measurements. The presence of other drugs and their interactions with lithium was rarely analyzed. Most of the studies proved that the duration of taking lithium (weeks – years) has no effect on its correlation regarding concentrations in saliva and serum. Differences between lithium ion concentrations in men and women were not observed, however, in the one study, a higher correlation between lithium levels in saliva and serum was found in women (Shetty 2012). Results regarding consistent measurements of lithium level in 1 patient (intrasubject) as well as in a group of patients (intersubject) are not clear-cut either. Some studies confirm concurrence in measurements of lithium concentrations in a patient as well as between patients.

Special attention should also be given to the fact that patients were taking different galenic forms of lithium as it may influence the results and clinical interpretation (Obach 1988).

CONCLUSION

Saliva in lithium level monitoring is promising biological material. However, the issue requires further studies basing on current data including methods of obtaining saliva and its biochemical analysis, collecting samples in a specific time frame from the last dosage of lithium as well as inter-subject or intra-subject measurements.

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Conflict of interest:

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