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Original Article

The impact of environmental temperature on lithium serum levels

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Objectives: Three studies have reported a seasonal variation in lithium serum levels, with higher levels during summer. Our objective was to investigate the impact of actual environmental temperature on lithium serum levels.

Methods: A retrospective study was conducted using available records of lithium serum levels for the period between January 1995 and July 2004, obtained from three large teaching hospitals in The Netherlands. Lithium serum levels were linked to season and average daily temperature data obtained from the Royal Netherlands Meteorological Institute. An analysis was performed on all lithium serum levels not accounting for the intra-individual dependency of lithium serum levels. The association between season, temperature and both absolute lithium serum level and the frequency of potentially toxic serum levels was investigated. A mixed model analysis, accounting for intra-individual dependency of lithium serum levels, was performed.

Results: A total of 41,102 lithium serum levels (3,054 patients) were included. A significant difference in mean lithium serum levels across seasons ($p < 0.001$) and temperature categories ($p = 0.001$) was found, peaking in summer [0.761 mmol/L, ± standard error of the mean (SEM) 0.002] and at temperatures of 15–20°C [0.762 mmol/L (± SEM 0.005)], and at a minimum in winter [0.748 mmol/L (± SEM 0.002)] and at <0°C [0.741 mmol/L (± SEM 0.005)]. The relative frequency of potentially toxic serum levels significantly differed between seasons ($p = 0.023$, highest in winter), but not between temperature categories ($p = 0.481$). A significant positive association for intra-individual lithium serum level and season ($p < 0.001$) and temperature ($p < 0.001$) was established.

Conclusions: Season and environmental temperature have a statistically significant but therapeutically irrelevant effect on lithium serum levels.

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Lithium is the most widely used drug in the management of bipolar disorder (BD), both in acute mania as well as in maintenance treatment (1). Its narrow therapeutic window (0.6–1.2 mmol/L), together with high intra- and interindividual variability in pharmacokinetics and interindividual sensitivity to adverse drug reactions, necessitates regular monitoring of lithium serum levels (2, 3). Lithium serum levels >1.3–1.5 mmol/L commonly result in toxic side effects (3, 4). The severity of symptoms is generally proportional to both the degree and the duration of the elevation of lithium serum levels (4).

Since about 80% of renally excreted lithium is reabsorbed in the proximal tubule together with

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sodium (5), any situation causing an increase in proximal reabsorption of sodium, such as a negative water or sodium balance (e.g., due to perspiration without adequate compensatory fluid and salt intake), will result in an increase in tubular lithium reabsorption, thereby elevating the lithium serum level and consequently the risk for lithium toxicity (2–4). Higher rates of perspiration can be induced, for instance, by fever, sudden changes in amount of exercise or sudden substantial elevations in environmental temperature (6–8).

To date, three studies have reported a seasonal variation in lithium serum levels, all reporting higher levels during summer. These studies were performed in different parts of the world, i.e., The Netherlands (9), Italy (10) and Michigan, USA (11). The differences in the extent of seasonal variation of lithium serum levels in the three studies were attributed to differences in environmental temperature in these different regions. For Italy, the observed seasonal variation was about 10% in a total of 168 patients, whereas in The Netherlands a difference of about 5% was observed in a total of 68 patients. In two of these studies the mean lithium serum level per patient for each season was studied. The study in Michigan evaluated the mean lithium serum level per month for a total of 377 admitted patients.

To our knowledge, the impact of actual environmental temperature on lithium serum levels, and the influence of season and actual environmental temperature on intra-individual lithium serum levels have never been studied. Therefore we investigated the impact of actual environmental temperature and season on lithium serum levels, taking within-subject dependency into account.

Methods

Setting and study population

A retrospective study was conducted using available records of lithium serum levels for patients in whom lithium serum levels had been measured in the laboratories of three large teaching hospitals in different parts of The Netherlands: TweeSteden Hospital, Tilburg; Altrecht Institute for Mental Health Care, Utrecht; and Reinier De Graaf Hospital, Delft. Data were gathered for the period between January 1995 and July 2004. Lithium serum levels for all patients aged ≥18 years for whom at least two levels were available were included.

Data on average daily temperature were obtained from the nearest meteorological site of the Royal Netherlands Meteorological Institute, all situated within 30 km of the respective laboratories.

Data

Data on patient gender, year of birth, lithium serum level and corresponding blood sampling date were gathered, along with a unique identification number for each patient. Approval to use anonymous patient data for this study was obtained from the scientific boards of the three participating institutions.

Lithium serum levels were linked to average daily temperature one day prior to blood sampling. Since blood samples are usually drawn in the morning and sodium and lithium serum levels can modify rapidly (2, 7, 8), the average daily temperature of the day prior to blood sampling was considered to be the most appropriate. Temperature was taken both as a continuous variable as well as a per 5°C categorized variable, with a lower category of temperatures <0°C and an upper category of temperatures ≥20°C.

In order to put the results into perspective with the results from the studies reported previously, the impact of seasonal variation on lithium serum levels was also investigated. Therefore, lithium serum levels were also linked to the different seasons, with seasonal transitions defined as occurring on March 21, June 21, September 21 and December 21, as in the previous studies.

Potentially toxic lithium serum levels were defined as levels ≥1.3 mmol/L, resulting from an increase ≥50% with at least two available preceding levels that fell within the therapeutic range (0.6–1.2 mmol/L). Age was categorized as old (≥65 years) and young (<65 years).

Data analysis

All lithium serum levels <0.2 mmol/L were excluded from analysis on account of uncertainty regarding the intake of lithium by the patient and analytical imprecision below this value.

Data analyses included every lithium serum level obtained from the subjects described in the paper. It is pertinent to note that these analyses potentially included several lithium levels for the same individual at different time-points and during different seasons of the year. Therefore, this analysis does not take into account within-subject (i.e., intra-individual) lithium levels. The mean lithium serum level, as well as the frequency of potentially toxic serum levels within each season and temperature category, were determined. The differences in mean lithium serum level between seasons and temperature categories were assessed by one-way ANOVA analysis. Differences in the frequency of potentially toxic serum levels across

seasons and temperature categories were analyzed by chi-square analysis.

In order to account for within-subject dependency of lithium serum levels, a linear mixed model analysis was subsequently performed. The coefficients 'season', 'temperature' and 'age' were defined as fixed effects (assuming that all variables of interest are represented in the data). A random intercept was used to allow for differences in intra-individual lithium serum levels.

All analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 41,102 lithium serum levels from a total of 3,054 patients were included. More females (62.3%) than males were included, and the mean age was 50.5 years [standard deviation (SD) 17.0]. A large variation in the total number of lithium serum levels per person was observed, with a median of 10 recorded levels per patient (range 2–100): 90% of the serum level measurements pertained to patients with up to 51 serum level measurements; 50% to patients with up to 28 serum level measurements; and 33% to patients with up to 14 serum level measurements. Lithium serum levels were equally distributed across seasons. However, with regard to temperature, about 75% of the levels were taken at 5–20°C (Table 1).

A statistically significant difference in mean lithium serum levels was found for seasons ($p < 0.001$), peaking in summer [0.761 mmol/L (± SEM 0.002)] and at a minimum in winter [0.748 mmol/L (± SEM 0.002)] (Fig. 1). The maximal seasonal difference in lithium serum level was about 2%. A statistically significant difference in mean lithium serum level for the temperature category ($p = 0.001$) was observed, with higher lithium serum levels occurring at higher average daily temperatures (Fig. 2). Mean lithium serum levels were 0.741 mmol/L (± SEM 0.005) at temperatures <0°C and 0.762 mmol/L (± SEM 0.005) at temperatures of 15–20°C, again resulting in a maximal difference of about 2%.

Table 1. Lithium serum level (n = 41,102) and temperature characteristics

Lithium serum levels	Season	n (%)	T (°C) Mean ± SD
Seasonal distribution	Spring	10,538 (25.6)	11.8 ± 4.5
	Summer	10,365 (25.2)	17.4 ± 3.1
	Autumn	10,073 (24.5)	8.1 ± 4.9
	Winter	10,126 (24.6)	4.5 ± 4.2
	T (°C)	n (%)	
Distribution per temperature category	<0	2,218 (5.4)	
	0–5	5,993 (14.6)	
	5–10	11,091 (27.0)	
	10–15	10,617 (25.8)	
	15–20	8,946 (21.8)	
	≥20	2,237 (5.4)	

T = temperature; SD = standard deviation.

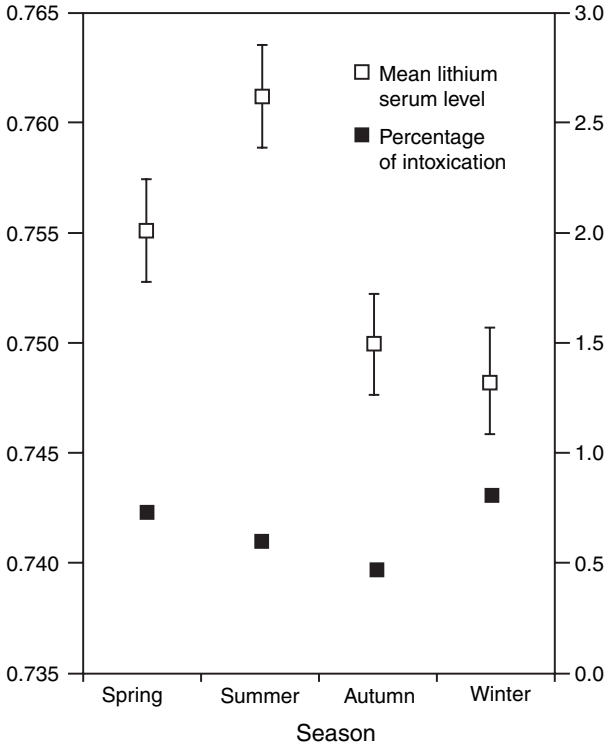

Fig. 1. Mean overall lithium serum levels (bars represent standard errors of the mean) and frequencies of potentially toxic serum levels [defined as a lithium serum level ≥1.3 mmol/L resulting from an increase ≥50% with at least two available preceding levels that fell within the therapeutic range (0.6–1.2 mmol/L)] per season. There was a statistically significant difference in mean lithium serum levels across seasons ($p < 0.001$, one-way ANOVA) and frequencies of potentially toxic serum levels ($p = 0.023$, χ^2) significantly differed between seasons.

A statistically significant difference in the frequency of potentially toxic serum levels ($p = 0.023$) across seasons was established (Fig. 1), with the highest frequency in winter, and the lowest in autumn. No significant ($p = 0.481$) difference was found in the frequency of potentially toxic serum levels across temperature categories (Fig. 2).

Taking into account the intra-individual dependency of the data, a statistically significant ($p < 0.001$) effect of both season and environmental temperature on lithium serum level was established by performing a mixed model analysis. Equations 1 and 2 represent the effect of season and temperature on lithium serum level, respectively:

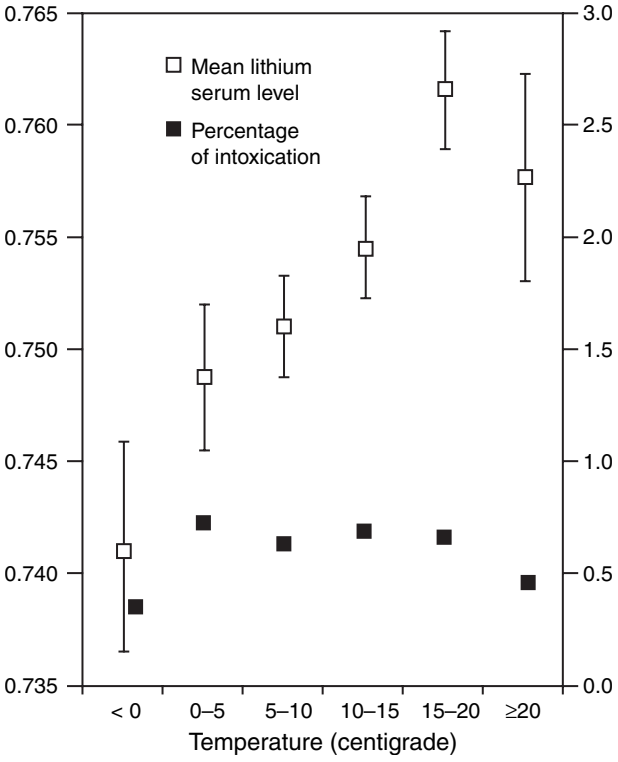

Fig. 2. Mean overall lithium serum levels (bars represent standard errors of the mean) and frequencies of potentially toxic serum levels [defined as a lithium serum level ≥1.3 mmol/L resulting from an increase ≥50% with at least two available preceding levels that fell within the therapeutic range (0.6–1.2 mmol/L)] per temperature category. There was a statistically significant difference in mean lithium serum levels across temperature categories ($p = 0.001$, one-way ANOVA). Frequencies of potentially toxic serum levels ($p = 0.481$, χ^2) did not significantly differ between temperature categories.

Equation 1:

$$\text{Lithium serum level (mmol/L)} = 0.00544\ (\text{SE } 0.00095) * \text{season}^1 + 0.722\ (\text{SE } 0.0036)$$

([1]substituting 1 for winter, 2 for autumn, 3 for spring and 4 for summer);

Equation 2:

$$\text{Lithium serum level (mmol/L)} = 0.000793\ (\text{SE } 0.000166) * \text{temperature}^2 + 0.727\ (\text{SE } 0.00321)$$

[[2]average daily temperature (°C) at one day prior to blood sampling].

Equation 1 results in lithium serum levels of 0.727 mmol/L and 0.744 mmol/L for winter and summer, respectively. Equation 2 results in lithium serum levels of 0.727 mmol/L at 0°C and 0.743 mmol/L at 20°C.

A sub-analysis on lithium serum levels was performed on a subset of patients for whom more than 6, more than 10, and more than 12 lithium serum levels were available. In these sub-analyses, the same trends were observed for the relationships between lithium serum levels and both temperature and season, respectively (results not shown).

In order to investigate the influence of age on the effect of temperature on lithium serum level, an age (young < 65 years and old ≥ 65 years) was included in the mixed model for temperature and lithium serum level. The effect of environmental temperature on lithium serum level was about twice as great in those aged ≥ 65 years (0.014 mmol/L elevation in lithium serum level per 10°C increase) than in those aged < 65 years (0.006 mmol/L elevation in lithium serum level per 10°C increase). This difference, however, was not statistically significant ($p = 0.065$).

Discussion

We found that lithium serum levels in daily clinical practice in The Netherlands showed statistically significant differences across seasons and temperatures. Higher lithium serum levels were observed at higher temperatures as well as during warmer seasons, the latter in accordance with results from previous studies (9–11). The effect of temperature and season on lithium serum level persisted when accounting for within-subject dependency of lithium serum levels.

Although statistically significant, the reported effects are not of clinical importance. A temperature increase of 10°C, for example, results in an elevation in lithium serum level of only 0.008 mmol/L (Equation 2). Although our finding that a warmer season is related to higher lithium serum levels is in accordance with results from previous studies, we report a maximal difference in lithium serum levels between seasons of about 2%, in contrast to the previously reported variation of about 5% in The Netherlands (9). This discrepancy may be explained by the fact that we included lithium serum levels for about 3,000 patients in contrast to the 68 patients included in the study by Beersma et al. (9). It may be possible to explain the observed difference in minimum and maximum serum level per season of 10% for Italy and 2% for The Netherlands in this study by the differences in climate between the two countries. Italy has a Mediterranean climate, characterized by dry, hot summers and mild winters. Compared to Italy, The Netherlands experiences overall lower temperatures without a dry season, due to lower summer temperatures and greater influence of the sea.

In addition, the frequency of potentially toxic serum levels did not differ statistically significantly

between temperature categories. A possible reason for this is that patients can avoid the consequences of high temperatures in summer via climate control measures (e.g., air conditioning) and through compensatory fluid and salt intake, as is recommended in information leaflets for patients taking lithium.

However, the frequency of potentially toxic serum levels did differ with statistical significance across seasons but, in contrast to our hypothesis on the impact of temperature on lithium serum levels, did not follow the order of coldest to warmest season. The observed peak during colder seasons may reflect a seasonal variation in the prevalence of intentional overdosing. Depression in BD has, in some studies, been shown to arise mostly in autumn and winter (12–15). The observed peak of potentially toxic serum levels may therefore possibly reflect a rise in suicide attempts corresponding with a higher prevalence of depression in winter. In the literature conflicting results are reported with respect to seasonal variation of intentional overdosing; most studies, however, report a peak in spring and summer (16–22). We cannot entirely explain the discrepancy between the peak in suicide attempts reported in the literature and the higher prevalence of potentially toxic serum levels in winter observed in this study. However, the reports in the literature with respect to seasonal variation and suicide frequency are conflicting and we have no information regarding the reasons for the observed potentially toxic serum level. It may be possible that, in our study, we missed several instances of intentional overdose and the corresponding lithium measurements, since one of the included hospitals is a psychiatric facility and patients with severe somatic problems due to intentional overdosing may have been transported to another (general) hospital. Due to a less adequately responding thirst center and a decreased glomerular filtration rate, elderly people are presumed to be more at risk for sudden elevation of lithium serum levels than younger people (23, 24). Accordingly, we did establish a trend towards a greater impact of temperature on lithium serum levels in elderly subjects.

There are several limitations to our study. First, in accordance with our hypothesis that environmental temperature has a prompt, if any, effect, we defined temperature as average daily temperature one day prior to blood sampling. In comparison with average daily temperatures over two-, three- and seven-day periods prior to blood sampling, temperature was defined as average daily temperature one day prior to blood sampling actually provided the best fit. We obtained data on average daily temperature, but maximal daily temperature, apparent temperature (25), or average daily temperature between dawn and sunset, instead of 24-h measurements, may also be of importance. Furthermore, it may be hypothesized that longer periods of elevated environmental temperature (e.g., heat waves) may have greater impact than short periods of elevated temperature.

Second, we had no information on lithium dosage. Bipolar disorder has been shown to display seasonal variation, possibly leading to prescriber-initiated dose changes and patient-initiated differences in adherence to treatment. Previous research has demonstrated evidence of seasonal variation in the course of BD, with mania arising more frequently in spring and summer, while depression tends to arise more in autumn and winter (12–15, 22, 26–30). Higher lithium serum levels in summer could therefore also be partly attributed to increases in lithium dose. On the other hand, it has been demonstrated that even at stable lithium doses, lithium serum levels fall during periods of mania and rise throughout periods of depression (31–34).

Third, we have no information on the specific reasons the lithium serum measurements were obtained. Measurements initiated because of suspected high levels caused by deliberate overdosing may not be excluded. It is possible that this may falsely influence the observed higher frequency of potentially toxic lithium serum levels.

Fourth, information on the time interval between blood sampling and last lithium intake was unspecified in most cases (93%). Time intervals of < 10 h distort correct interpretation of measured lithium serum levels by presenting falsely high values due to an incomplete distribution phase (2). This could also falsely influence the observed higher frequency of potentially toxic lithium serum levels since it can be expected that, in cases of suspected overdose, the regime of a 12.0 ± 0.5 h time interval is often not followed. However, because all laboratories claimed to have structured a 12.0 ± 0.5 h time interval regime in accordance with the guideline (35), most time intervals were probably > 10 h.

Finally, we have not been able to correct for other important patient characteristics that have previously been demonstrated to be related to lithium serum levels, such as comorbidity, current mood phase of BD, diarrhea, vomiting, infections or renal insufficiency, concomitantly used medication, pregnancy, changes in diet, alcohol use or weight, and higher rates of perspiration due to exercise or visits to saunas (2, 36–38).

In conclusion, our results show that environmental temperature has a statistically significant but therapeutically irrelevant impact on lithium

serum levels. The lack of any clinically relevant impact of both season and temperature may possibly be explained by adequate measures taken by both clinicians and patients in response to changes in environmental temperature.

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