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BIPOLAR DISORDERS

Original Article

Drug-drug interactions as a determinant of elevated lithium serum levels in daily clinical practice

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Objective: Lithium is a drug with a narrow therapeutic window. Concomitantly used medication is a potentially influencing factor of lithium serum concentrations. We conducted a multicentre retrospective case-control study with the aim of investigating lithium-related drug interactions as determinants of elevated lithium serum levels in daily clinical practice.

Methods: Cases were patients with an increase of at least 50% in lithium serum concentrations resulting in an elevated lithium serum level of at least 1.3 mmol/L, and who were not suspected of a suicide attempt. Controls were patients who showed stable lithium serum levels within the therapeutic range. Use and start of non-steroidal anti-inflammatory drugs, diuretics, renin–angiotensin inhibitors, theophyllin and antibiotics were investigated as potential determinants of the elevated lithium serum levels. Irregularity in lithium dispensing pattern, change in lithium dosing regimen, age, gender, prescribing physician and laboratory parameters were investigated as potential confounders.

Results: We included 51 cases and 51 controls in our study. Five (9.8%) controls and 15 (29.4%) cases used potentially interacting co-medication [OR of 3.83 (95%CI 1.28–11.48)]. Start of potentially interacting co-medication was observed in eight (15.7%) cases and in zero (0%) controls resulting in an OR of 20.13 (95% CI 1.13–359). After adjustment for co-medication, irregularity in lithium dispensing pattern, change in lithium dosing regimen, and age, the statistically significant association was lost. We report an OR of 2.70 (95% CI 0.78–9.31) for use of concomitant medication, with a large contribution of antibiotic agents, and an OR of 3.14 (95% CI 1.15–8.61) for irregularity in lithium dispensing pattern.

Conclusion: Use of co-medication, especially antibiotics, tends to be associated with elevated lithium serum levels.

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Lithium salts are first choice agents for the long-term prophylaxis and acute treatment of several psychiatric disorders (1–3). A strong relationship between lithium serum levels and both its efficacy and its toxicity has been established (4–8). The narrow therapeutic window together with the high inter- and intra-individual variability in pharmacokinetics and sensitivity to its effects, necessitates regular therapeutic drug monitoring of patients receiving lithium (8–10). Guidelines for monitoring lithium serum levels have been developed worldwide. In the Netherlands, for example, it is recommended to measure lithium serum levels at a frequency of two to four times a year after stable

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therapeutic lithium serum levels (0.6–1.2 mmol/L) have been reached (11).

A large part of the intra-individual variability in lithium pharmacokinetics is due to the high susceptibility of lithium excretion to changes in renal blood flow and water and salt homeostasis. Influencing factors include somatic comorbidity (e.g. water and electrolyte changes induced by fever, diarrhoea or vomiting) and concomitantly used drugs [e.g. nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics and renin–angiotensin (RAS) inhibitors]. For most of these drugs a mechanism explaining the interaction with lithium excretion has been either proposed or fully elucidated.

Non-steroidal anti-inflammatory drugs increase lithium serum concentrations by inducing a decrease in glomerular filtration rate as a result of inhibition of prostaglandin synthesis. Diuretics influence lithium serum concentrations by inducing sodium depletion and thereby stimulating proximal sodium and therefore lithium reabsorption. RAS inhibitors induce volume depletion and in this manner reduce glomerular filtration rate, which may lead to a reduction in lithium clearance. Up to now, theophyllin has been implicated in lowering lithium serum concentrations by inducing lithium clearance through an unknown mechanism. The interaction between antibiotics and lithium is most likely not directly related to the drug itself but probably related to the fever, vomiting, diarrhoea and poor food and water intake associated with the underlying infection.

Most of the drug-drug interactions mentioned in textbooks and other sources of clinical information originate from case reports and small controlled studies (12–38). The actual relevance of drug-drug interactions with lithium in daily clinical practice, to our knowledge, is unknown. Therefore, relying on the established relationship between lithium serum concentrations and risk of (toxic) side-effects, we conducted a study to determine the influence of concomitant medication on the development of elevated lithium levels.

Methods

Setting

A multicentre retrospective case–control study was conducted among patients receiving long-term treatment with lithium for whom lithium serum concentrations were under hospital laboratory control, during the time period of January 1997 until January 2003. Lithium serum concentrations of both inpatients and outpatients in the Netherlands are usually monitored by hospital laboratories. A total of 12 teaching hospitals participated in the study.

The medical ethics committee of the St Radboud University Hospital in Nijmegen, The Netherlands, approved the study protocol.

Study population

The study base consisted of patients who were at least 18 years of age and on lithium treatment for at least 3 months. To be eligible for participation all participants (cases and controls) had to have at least two subsequent lithium serum concentrations within the therapeutic range (0.6–1.2 mmol/L). Blood samples had to be drawn at least 10 h after the last lithium intake. Both inpatients and outpatients were eligible for participation. Patients were excluded if they were suspected of a suicide attempt.

From this study base we identified all cases and sampled controls as displayed in Figure 1. Cases were defined as all patients with a lithium serum level of $\geq$1.3 mmol/L, in combination with an increase in lithium serum level of at least 50% compared with the previous lithium serum level. The date on which the elevated lithium serum level was encountered was termed the 'index date'. For each case one control was randomly selected from the aforementioned study base. Controls had to have a lithium serum level on the case index date ($\pm$1 week) within the therapeutic range (0.6–1.2 mmol/L). In addition, the difference between the lithium serum level on the index date and the previous lithium serum level had to be $<$ 50%. For both cases and controls, the time window between the index date and the date of lithium serum level determination prior to the index date had to be $<$ 6 months.

Exposure definition

Exposure to potentially interacting concomitant medication in both the cases and the controls was assessed. From the literature, four drug classes (NSAIDs, diuretics, RAS inhibitors and antibiotics) and theophyllin were *a priori* identified as potentially interacting with lithium. Although strictly speaking the interaction with antibiotics is not a drug-drug interaction, but a drug-disease interaction, antibiotics were included.

Information on the study groups' exposure to these potentially interacting drugs was collected from drug dispensing data obtained from the 'community pharmacy', hospital pharmacy or the general practitioner's medical record. Drug

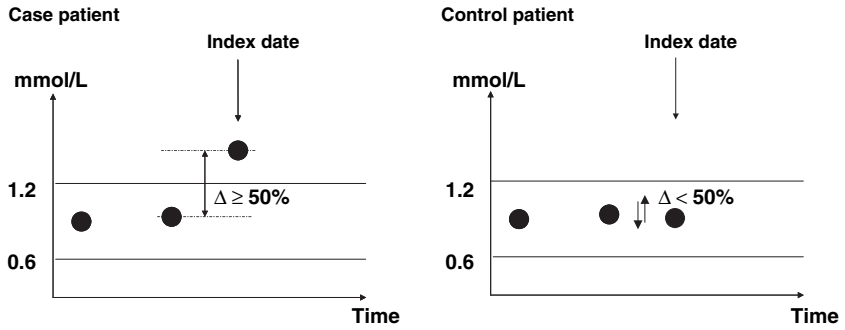

Fig. 1. Case and control definition. Case: patient with an elevated lithium serum concentration (≥1.3 mmol/L) resulting from an increase of at least 50% compared with the previous lithium serum concentration. The date on which this lithium serum concentration was encountered is termed the index date. Control: patient who on the index date had a lithium serum concentration within the therapeutic range (0.6–1.2 mmol/L), not encompassing a difference of >50% compared with the lithium serum concentration prior to the one encountered on the index date.

dispensing data was obtained for a period starting at least 1 year prior to the index date. For each drug dispensed, the prescription filling date, the drug name, the daily amount of drug prescribed and the total amount of drug per prescription was provided. In order to determine the theoretical exposure time window, the total amount of drug dispensed per prescription was divided by the daily amount of drug prescribed. Patients were considered users if the medication was started before the index date and the index date fell within the theoretical exposure window. Starting and stopping of potentially interacting drugs are considered the most critical events on the subject of drug-drug interaction. Therefore we also looked into a subpopulation of users of medication, specifically those who had recently started on concomitant medication. Starting was defined as having had a first prescription in the 30-day period before the index date and not having had a prescription for the same medication in the 120 days before this 30-day period. For use of NSAIDs and antibiotics, starting was defined as having had a first prescription for the medication in the 30 days prior to the index date and not having had a prescription for a drug of the same drug class in the 14 days prior to the start of the drug before the index date. This difference in definition for starting on NSAIDs and antibiotics was chosen because influences of NSAIDs or antibiotics are known to appear and disappear rather quickly. Both NSAIDs and antibiotics can be used for relatively small periods, whereas diuretics and RAS inhibitors often are used for longer periods.

Potential confounding factors

In order to adjust for any factor that may confound the association between the use of concomitant medication and the occurrence of elevated lithium levels, the following data were gathered from the medical record and laboratory history: patient characteristics (age, gender), prescribing physician (psychiatrist or other), change in lithium dosing regimen (type of salt, daily dose and dose frequency) and laboratory parameters (serum creatinine, sodium, thyroid-stimulating hormone and potassium concentrations). In addition, irregularity in lithium dispensing pattern per patient was estimated using the pharmacy dispensing data for a time period encompassing at least three different dispensing occurrences before the index date (39). Dispensing was termed irregular if the calculated ratio – days for which medication was dispensed according to dispensing data (the total dispensed amount divided by the prescribed daily dose) divided by the total number of days encompassing the time period – was <90% or >110%.

Data analysis

Difference in baseline population characteristics between case subjects and controls was evaluated with Mann-Whitney and with chi-square analysis where appropriate.

The primary determinants (use and starting of potentially interacting concomitant medication) and all variables considered to be potentially confounding factors were assessed for the presence of a statistically significant association with elevated lithium serum levels by performing a univariate logistic regression analysis.

Those variables that were univariately significantly associated with elevated lithium serum levels ($p < 0.10$) and that caused a change in point estimate of ≥10% were incorporated into our multivariate model.

In order to assess the OR for determinants or potential confounding factors for which either in the cases or the controls, zero was included in the 2×2 table 0.5 was added to all data.

Data were analysed using SPSS version 11.0.

Results

Fifty-one cases and 51 controls were included in the study. Population characteristics (age, gender) as well as the distribution of variables among cases and controls are presented in Table 1.

Although cases were slightly older than controls and females were represented more frequently, age and gender differences were not statistically significant. For cases the increase in lithium serum level between the index date and the date prior to the index date was 107% (range: 50–369%). For controls this change was −2.4% (range: −30.6% to 42.3%). The lithium serum level on the index date was 1.6 mmol/L (range: 1.3–2.8 mmol/L) versus 0.8 mmol/L (range: 0.6–1.1 mmol/L) for cases and controls respectively. No statistically significant changes in lithium salt and change in lithium dosage were found. Cases and controls differed significantly for the number of days that had elapsed between the index date and the date prior to the index date.

Irregularity in lithium dispensing pattern, according to our definition (based on pharmacy dispensing data), was determined for 83 of the 102 patients in our study population. The remaining 19 of the 102 patients in our study population were inpatients for whom medication was delivered to the ward, exclusively based on prescription refill data.

For 13 patients in our study population, the prescribing physician could not be identified based on medication dispensing data. Laboratory parameters measured within a range of 3 days prior to or after the index date were not broadly available. Therefore data on laboratory parameters could not be taken into account for in our analysis.

Five (9.8%) controls and 15 (29.4%) study subjects used potentially interacting co-medication

Table 1. Characteristics of the study population

	Controls (n = 51)	Cases (n = 51)
Patient characteristics		
Female gender, N (%)	30 (58.4)	36 (70.6)
Age, mean (SD)	49.8 (13.8)	54.9 (15.0)
Lithium characteristics		
Prescribing physician [psychiatrist, N (%)]	32 (68.1)	32 (72.7)
Irregularity in lithium dispensing pattern ≥110% or <90%	**9 (21.0)**	**19 (47.5)**
Change in lithium dosing regimen (change in daily intake frequency and/or change in lithium salt and/or change in prescribed daily dose, N (%)	8 (15.7)	9 (17.6)
Index date parameters		
Lithium dose (mmol/24 h), median (range)	27 (10.8–43.2)	27 (10.8–43.2)
Lithium serum level (mmol/L), median (range)	**0.80 (0.59–1.1)**	**1.55 (1.28–2.78)**
Date prior to the index date parameters		
Lithium dose (mmol/24 h), median (range)	27 (10.8–43.2)	27 (10.8–43.2)
Lithium serum level (mmol/L), median (range)	0.83 (0.59–1.2)	0.78 (0.56–1.16)
Change between index date and date prior to the index date		
Lithium serum level elevation (%), median (range)	**–2.39 (–30.6–42.3)**	**107 (49–369)**
Number of days, median (range)	**90 (7–168)**	**42 (3–197)**
Concomitantly used medication, N (%)		
Use of interacting medication	**5 (9.8)**	**15 (29.4)**
NSAID user	2 (3.9)	2 (3.9)
Diuretic user	2 (3.9)	6 (11.8)
RAS inhibitor user	3 (5.9)	4 (7.8)
Antibiotic user	0 (0)	7 (13.7)
Starting of concomitant medication	**0 (0)**	**8 (15.7)**
NSAID starter	0 (0)	1 (2.0)
Diuretic starter	0 (0)	1 (2.0)
RAS inhibitor starter	0 (0)	1 (2.0)
Antibiotic starter	0 (0)	7 (13.7)

Values in bold indicate a statistically significant difference between study subjects and controls established in a univariate logistic regression analysis.

Table 2. Univariate and multivariate logistic regression analysis

	Univariate analysis		Multivariate analysis	
	OR	95% CI	OR	95% CI
Use of concomitant medication	3.83	1.28–11.48	2.70	0.78–9.31
Starting of concomitant medication	20.13[a]	1.13–359	n.e.	n.e.
Irregularity in lithium dispensing pattern	3.42	1.31–8.94	3.14	1.15–8.61
Age (continue)	n.e.	n.e.	n.e.	n.e.
Change in lithium dosing regimen	1.15	0.41–3.27	1.38	0.45–4.24

n.e. = not able to estimate.
[a]To assess the OR for determinants or potential confounding factors for which either in the cases or the controls, zero was included in the 2×2 table and 0.5 was added to all data.

resulting in an OR of 3.83 (95% CI 1.28–11.48). Starting of potentially interacting co-medication was observed in zero (0%) controls and eight (15.7%) study subjects resulting in an OR of 20.13 (95% CI 1.13–359) (Table 2).

As can be seen in Table 1 the largest contribution of potentially interacting concomitant medication in both users and starters can be attributed to the class of antibiotics. Seven cases and no controls were users of antibiotics. Within the cases six different antibiotics were used. No specific antibiotic, thus, seemed to be more associated to elevated lithium serum levels. Irregularity in lithium dispensing pattern, calculated for 83 of the 102 patients in our study population, was clearly associated with elevated lithium serum levels (OR 3.42, 95% CI 1.31–8.94).

Potential confounding for the calculated OR for use of potentially interacting concomitant medication was dealt with in our multivariate analysis. Irregularity in lithium dispensing pattern, change in lithium dosing regimen (both significant confounding agents according to our definition) and age were incorporated into our multivariate analysis. The association between the use of concomitant medication and elevated lithium serum levels lost statistical significance upon performing the multivariate analysis (OR 2.70, 95% CI 0.78–9.31). Irregularity in lithium dispensing pattern was found to be statistically significant when associated with elevated lithium serum levels (OR 3.14, 95% CI 1.15–8.61).

Discussion

Our results show that the use and start of potentially interacting concomitant medication is associated with elevated lithium serum levels in daily clinical practice. Unfortunately in our multivariate analysis the statistical significance of the association is lost. Within the drug groups no specific drug seemed to be more associated with elevated lithium serum levels.

As there were no starters among our controls, performing a multivariate analysis on starting of concomitant medication was not possible.

Our results further indicate that irregularity in lithium dispensing pattern is an important risk factor for elevated lithium serum levels, as we found a statistically significant association between elevated lithium serum levels and an irregular lithium dispensing pattern.

There are certain limitations to our study. We only gathered data on elevated lithium serum levels and no data on the actual appearance of (toxic) side-effects of lithium. However, a strong relationship does exist for lithium serum concentrations and the risk of appearance of (toxic) side-effects. Furthermore, we did include an increase in lithium serum level of at least 50% relative to the prior measured level, which for an individual stabilized on lithium is associated with a high risk of the appearance of (toxic) side-effects (4–10).

We had no access to information on possible concomitant use of over-the-counter medication. Such information could be important, particularly in case of NSAIDs (12, 15, 16, 26, 27, 32–36), which are, in the Netherlands for example, freely accessible.

Besides use and start of potentially interacting co-medication, the withdrawal of these agents could also influence lithium serum levels. However, it has been reported that withdrawal is more likely to result in a decrease (12–38) rather than in an increase in lithium serum level. As our focus is on the appearance of elevated lithium serum levels, data on withdrawal of potentially interacting drugs was of lesser importance to this report.

The most plausible explanation for the association between the use of antibiotic agents and elevated lithium serum levels lies with the underlying infection, associated fever and poor fluid intake. Therefore, missing data on somatic comorbidity associated with fever and poor fluid intake could be of great importance.

Laboratory parameters are known to fluctuate rather quickly. Therefore we allowed a maximum of only 3 days between the index date and the date at which the laboratory parameter was determined. Our rather stringent criteria may have resulted in the lack of laboratory parameters. As lithium clearance is largely influenced by disturbances in electrolyte and fluid homeostasis and renal function, missing data on laboratory parameters could be of considerable importance.

We do not have any information on environmental temperature. Besides the influence of endogenous temperature (provided for example by fever), there is also evidence for the influence of exogenous temperature (environmental temperature) on lithium serum levels (40).

Finally the small sample size is a limitation. It might be possible that the appearance of elevated lithium serum concentrations (according to our definition) and the use of potentially interacting concomitant medication are not as frequently present as thought in advance.

The strength of our study is that we evaluated the importance of lithium-related drug-drug interactions on elevated lithium serum levels, not in a research setting, but in daily clinical practice. To our knowledge, this study is the first to evaluate drug-drug interactions with lithium as a determinant for elevated lithium serum levels in daily clinical practice. Drug prescribing physicians, knowledge of drug dispensing pharmacists and patient's experience on handling of potential drug-drug interactions and symptoms is as such taken into account. Moreover, as our study was performed as a multicentre study we are not constrained by regional differences in prescription and treatment guidelines.

For both use and start of potentially interacting concomitant medication, the class of antibiotics is shown to be the most important contributor. Within the group of antibiotics, no specific antibiotic seemed to be more associated to elevated lithium serum levels. In the Netherlands the 'community pharmacy' performs checks on the concomitant prescription of potentially interacting drugs with lithium, it verifies concomitant prescription of diuretics, RAS inhibitors, NSAIDs and metronidazol (41). One can imagine that the check on the concomitant prescription next to lithium, and the following warning signal generated by the 'community pharmacy' does lead to extra caution in both physician and patient. However, for concomitant prescription of antibiotics next to lithium no such warning signal is generated. In addition, it is possible that in case of use of antibiotic agents by the patient, some symptoms associated with lithium (toxic) side effects can be misinterpreted and consequently be wrongly attributed to the infection.

The potential of several drugs to decrease lithium clearance has been shown. However, evidence for clinical relevance of lithium-related drug interactions resulting in either induction or inhibition of lithium clearance is inconclusive (12, 22).

In conclusion, in this population-based case–control study we found that in daily clinical practice co-medication and especially antibiotic agents tend to be associated with a higher risk of elevated lithium serum levels. In addition, the association between irregularities in lithium dispensing patterns is a risk factor for elevated lithium serum levels. Based on the results of our study we would like to make two recommendations: first, careful monitoring of lithium dispensing characteristics at the 'community pharmacy' and of the prescribed amount of lithium by the prescribing physician; secondly, considering extra lithium serum concentration monitoring for those suffering from an infection. Use of antibiotics can, as such, be considered a proxy for the existence of an infection. Based on the large contribution of antibiotic agents, further studies on the effects of concomitant prescription of these agents next to lithium are warranted.

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