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SHORT COMMUNICATION

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Is polarity of recurrence related to serum lithium level in patients with bipolar disorder?

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Abstract *Background* Recently published data might indicate that the polarity of recurrence is related to lithium serum levels. To systematically test this hypothesis all published maintenance trials in bipolar disorders were examined with regard to this issue. *Method* Maintenance studies were subdivided in trials with low (i. e. below 0.6 mEq/l), medium (i. e. 0.6 to 0.8 mEq/l) and high (i. e. above 0.8 mEq/l) lithium serum levels. Percentage of depressive vs. (hypo-)manic or mixed recurrences were compared for these three groups. *Results* The percentage of depressive recurrences in the groups with low, medium and high lithium levels differed in a clinically and statistically significant manner (12 % vs. 38 % vs. 64 %, $p < 0.0001$). *Conclusion* The results might indicate that low lithium levels are effective in preventing depression whereas higher blood levels are needed to prevent (hypo-)manic or mixed states.

Key words bipolar disorder · drug dose response relationship · lithium · review

Introduction

The three latest randomized clinical trials (RCTs) in long-term treatment of bipolar disorders were primarily designed to establish lamotrigine and olanzapine as mood-stabilizers (Calabrese et al. 2003; Bowden et al. 2003; Tohen et al. in press). However, these studies also changed the appraisal of prophylactic lithium treatment. First, they demonstrated that lithium continues to be an excellent treatment option for the prevention of affective episodes in a study design that is up to modern methodological standards. Second, these new studies raise the question whether a specific mood-stabilizer might rather prevent the depressive pole, or the manic pole of the illness. With respect to lithium the studies seem contradictive at first sight. Both lamotrigine trials suggest that lithium has its strength against the manic pole of the illness. The olanzapine trial however primarily supports lithium's prophylactic antidepressive properties (for details cf. Severus et al. submitted). This might, at least partly, be related to a different spectrum of efficacy of the substances to which lithium was compared. An alternative explication would be that the contradictory results are related to the different lithium serum levels used in these studies. Lithium seems effective at preventing depression at a mean serum level of 0.73 mEq/l (Tohen et al. in press) and seems efficacious in preventing manic or mixed states in the range of 0.8 to 1.1 mEq/l (Calabrese et al. 2003; Bowden et al. 2003). This finding is in line with other reports which support the idea that low lithium levels are needed to prevent bipolar depression and high lithium levels to prevent mania (for details cf. Kleindienst et al. submitted).

We hence reviewed the published clinical trials with regard to this question. Our hypothesis was that the percentage of depressive (vs. (hypo-)manic or mixed) recurrences would clearly differ according to the mean lithium serum levels in maintenance trials published from 1966 to November 2004.

Methods

Localization of trials was based on a Medline search limited to "Randomized Controlled Trials" or "Clinical Trials" in adult humans, using the MeSH Terms "bipolar disorder" and "lithium". The computer based identification of trials was complemented by an extensive hand search. Studies were included if they had an observation period of at

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least six months and used lithium monotherapy as the prophylactic agent.

A total of 19 relevant studies were identified and included in the following analysis (Bowden et al. 2000, 2003; Calabrese et al. 2003; Coppen et al. 1976; Cundall et al. 1972; Gelenberg et al. 1989; Hartong et al. 2003; Johnston et al. 1980; Kane et al. 1982; Kocsis and Stokes 1979; Lusznat et al. 1988; Mendlewicz et al. 1973; Persson 1972; Prien et al. 1973, 1984; Quitkin et al. 1981; Stallone et al. 1973; Tohen et al. in press; Waters et al. 1982).

The trials were subdivided into studies with low, medium and high lithium serum levels (below 0.6 mEq/l vs. 0.6 to 0.8 mEq/l vs. over 0.8 mEq/l). Under the null hypothesis we would expect an equal percentage of depressive vs. manic or mixed recurrences in each of the three groups. The association between serum level and polarity of recurrence was evaluated using Mantel-Haenszel statistics. Total numbers of depressive vs. (hypo-)manic or mixed recurrences were compared using the sign test.

Results

We recorded 377 recurrences in the 19 studies that reported the polarity of recurrence. In general, (hypo-)manic or mixed recurrences tended to be slightly more frequent than depressive recurrences (217 vs. 170, $p = 0.063$).

Lithium levels were clearly related to the polarity of recurrence ($\chi^2(1) = 45.27$, $p < 0.0001$, see Fig. 1). Depressive episodes were relatively frequent in the group with high lithium levels (64% of the recurrences were depressive in this group) but rare in the group with low lithium levels (only 12%). The medium group (lithium levels between 0.6 and 0.8 mq/l) was also in the middle with respect to percentage of depressive recurrences (38%, see Fig. 1).

Discussion

The results of our analysis clearly indicate that the polarity of recurrence (depressive vs. manic or mixed) highly depends on the lithium blood level. Low lithium levels might better prevent depressive than (hypo-)manic or mixed states. Inversely, higher lithium levels might be effective in preventing (hypo-)manic or mixed states.

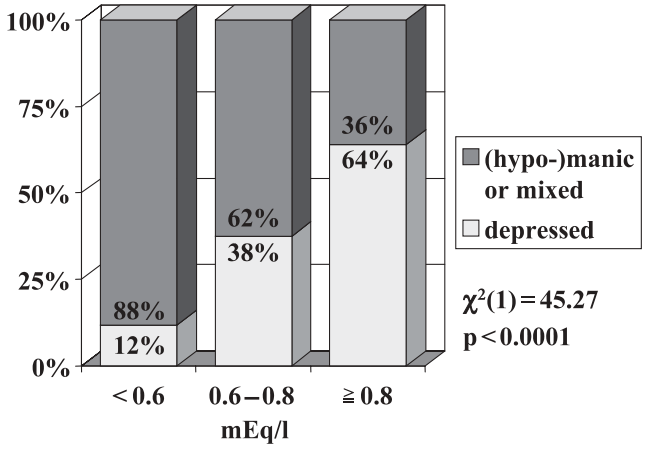

Fig. 1 Percentage of depressive vs. (hypo-)manic or mixed recurrences in patients with low (n = 43), medium (n = 184) and high (n = 150) lithium levels

This review has several limitations which need to be addressed. The studies reviewed are very heterogeneous as to the study design and patient population. In most of the studies plasma levels are only available as mean values or target ranges. It is therefore impossible to exclude the possibility that the results from this review have been influenced by stratification effects and confounding variables. For instance, over the last three decades, a significant shift has taken place in both the patients included in clinical trials and the recommended lithium levels. In the 1970s most patients with bipolar disorder enrolled in clinical trials had a history of at least one full-blown manic episode. At the same time lithium levels used in these trials tended to be relatively high. Consequently patients prone to mania tended to be maintained on relatively high serum levels. Similarly, a multitude of other confounders could be discussed, which are impossible to control for and therefore have to be regarded as a serious limitation to the result presented in this review.

The only reliable way to overcome such confounders and limitations is to relate lithium levels to polarity of recurrence within a trial. In order to address this question, in summer 2004 we contacted major research groups who have recently carried out RCTs implying prophylactic lithium (Bowden et al. 2000; Calabrese et al. 2003; Perlis et al. and Tohen et al. in press). A collaborative analysis of the data is underway but results are not fully available yet. In the meantime we have to rely on the two published lithium trials relating different serum levels within the trial to subsequent manic and depressive recurrences. Kocsis and Stokes (1979) report significantly lower lithium levels during the three-month periods preceding manic episodes than during the periods preceding depressive episodes (0.47 vs. 0.64 mEq/l) and hence fully support the major finding of this review. However, as patients were not randomized to a specific lithium level, this finding could well result from other potential confounders already discussed above. Consequently, from a methodological point of view the evidence provided by the study by Gelenberg et al. (1989) is the strongest available today as patients were randomized to two different ranges of plasma lithium levels. Again, the probability for a manic or mixed relapse/recurrences was clearly related to the lower range of lithium levels (0.4–0.6 mEq/l). This result is statistically significant as has been shown in a recent review (Severus et al. submitted).

While the results of this trial are compatible with (and even suggestive of) the idea that low lithium levels might be more effective against depressive than against (hypo-)manic or mixed states, they do not prove it. The analysis we performed exclusively deals with the percentage of depressive versus manic/mixed episodes at a given lithium serum level. It does not tell anything about the total number of both depressive and manic/mixed

episodes. For example, we cannot exclude the possibility that, although the relative percentage of depressive episodes is highest in the high serum lithium level group, the absolute number might be very small. This scenario could happen if the total number of manic episodes is extremely small at high lithium levels. Consequently the relative percentage of depressive episodes would necessarily increase, even if the absolute number of depressive episodes also decreases at high lithium levels.

In summary the available evidence indicates that prophylactic lithium has a distinctly different spectrum of efficacy depending on the precise lithium serum level. If this result could be further corroborated by a more rigorous approach that excludes or controls for major confounders, this finding might well change our approach with regard to the use of lithium in the prophylactic treatment of bipolar disorder.

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