



Effect of Hypertension on Blood Lithium Level and its Concentration to Dose Ratio in Manic Episode Patients

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ABSTRACT

The objective of this study was to further explore the influence of hypertension on blood lithium levels and its concentration to dose ratio (C/D) in patients with manic episodes. A total of 112 patients with manic episodes from the Wuhan Wudong Hospital between July 2021 and December 2022 were assigned into a control group (CG) and a hypertension group (HG). The patients' blood lithium concentrations, blood lithium C/D ratios, antihypertensive medication use, Young Mania Rating Scale (YMRS) scores, adverse reactions (ARs), and other parameters were monitored and compared. The average blood lithium concentration in the CG was 0.78 ± 0.27 mmol/L, and the average blood lithium C/D ratio was 0.91 ± 0.43 mmol·L⁻¹·g⁻¹·d, which were remarkably inferior to those (0.89 ± 0.20 mmol/L and 0.97 ± 0.46 mmol·L⁻¹·g⁻¹·d) in the HG. Further subgroup analysis based on antihypertensive medication revealed a drastic increase in blood lithium C/D ratio in the calcium channel blocker (CCB) subgroup. After the treatment, the YMRS score was 7.84 ± 0.82 in the CG and 9.12 ± 0.89 in the HG. The total number of ARs in the HG was superior to the CG, and the occurrence of ARs in both groups was concentrated within 3-15 days, accounting for 48.6% of all ARs. Patients in the HG had higher blood lithium concentrations, slower lithium metabolism, and a higher risk of ARs versus the CG. It was concluded that further investigation is warranted to explore the underlying mechanisms of these effects.

INTRODUCTION

Patients with manic episodes are a unique population characterized by elevated mood that is disproportionate

to their circumstances. According to the latest report, there are approximately 245 million hypertensive patients in China, representing a 41.5% increase compared to the previous national survey. The incidence of hypertension in patients with manic episodes is 2-3 times higher than that in the general population, and studies have shown an increasing prevalence of hypertension among patients with manic episodes (Schiweck *et al.*, 2021). Lithium carbonate, as a mood stabilizer, is widely applied in the treatment of patients with manic episodes, exhibiting notable antimanic effects and mild antidepressant effects. Nevertheless, lithium carbonate has a narrow therapeutic window, with a close proximity between therapeutic and toxic doses. Moreover, there is considerable inter-individual variation

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Authors' Contribution

DL and ML contributed equally to this work as co-first author. DL, ML, ZX and XG conducted the experiments in this study. QJ, YX, BL and XG contributed to the design and interpretation of the current study and wrote the article. All authors read, revised, and approved the final manuscript.

Key words

Hypertension, Manic episodes, Blood lithium, Clearance/dose ratio

in blood drug concentrations, leading to a high incidence of adverse drug reactions (Ithman *et al.*, 2018; McIntyre and Calabrese, 2019). Hence, the treatment of patients with comorbid hypertension and manic episodes using lithium carbonate becomes more complex and variable. Patients with comorbid hypertension and manic episodes not only exhibit physiological differences compared to ordinary patients but also receive a variety of antihypertensive drugs with different mechanisms of action, which can affect lipid metabolism, glucose metabolism, renal function, and other physiological processes (Beunon *et al.*, 2021; Liakos *et al.*, 2019; Li *et al.*, 2023). Hence, medication selection should be tailored to each patient's specific condition. The aim of this study was to explore the influence of hypertension on blood drug concentrations in patients with manic episodes, as well as to investigate the patterns and characteristics of adverse drug reactions. The findings will provide new insights for the clinical treatment of patients with manic episodes and serve as a reference for the safer use of lithium carbonate in clinical practice.

MATERIALS AND METHODS

General information

A total of 112 patients with manic episodes were selected from the Wuhan Wudong Hospital between July 2021 to December 2022. Based on the presence or absence of hypertension, the patients were rolled into a control group (CG) and a hypertension group (HG), with 56 patients in each group. Patients in both groups were eligible to join the study if they met the following inclusion criteria: Confirmed as a manic patient according to the 10th International Classification of Disease-10 (ICD-10), the patient took Lithium carbonate for treatment and was more than one week away from the last treatment, lithium carbonate blood concentration monitoring in the hospital, the patient had clear consciousness and voluntarily cooperated with the study, and complete patient medical record information. Pregnant or lactating women, patients with liver and kidney dysfunction, individuals with severe physical diseases or brain lesions and substance abuse or dependence, patients who had received electric shock or transcranial magnetic stimulation treatment in the past six months and incomplete case information were excluded from the study.

The CG consisted of 27 males and 29 females, with an age range of 22 to 68 years, averaging 43.53±4.32 years. The average body mass index (BMI) was 23.83±2.05. The HG consisted of 30 males and 26 females, with an age range of 24 to 67 years, averaging 43.73±4.76 years. The average BMI was 24.12±2.84. The inclusion and exclusion criteria for patient selection are detailed in Tables I. The

baseline characteristics of the two groups were comparable and showed no considerable differences ($P<0.05$). This study was approved by the Ethics Committee of our hospital, and all patients were informed about the treatment procedures and necessary monitoring parameters. Written informed consent was obtained from all patients included in the study.

Table I. Effect of hypertension on adverse reactions (ARs) over a period of 15 days in manic episode patients.

Group	<3d	3~15d	>15d	Total
CG	3(8.6)	6(17.1)	5(14.3)	14(40.0)
HG	4(11.4)	11(31.4)	6(17.1)	21(60.0)
Total	7(20.0)	17(48.6)	11(31.4)	35(100.0)

CG, control group; HG, hypertension group.

Therapeutic methodologies

Both groups of patients received lithium carbonate treatment, taking lithium carbonate tablets (manufactured by Hunan Qianjin Xiangjiang Pharmaceutical Co., Ltd., approval number: H43020372, specification: 250 mg/capsule). The recommended initial dose was 500 mg/day, which could be taken orally three times a day after meals. From the second week onwards, the lithium carbonate dosage was gradually increased. Therapeutic drug monitoring was employed to control the patients' blood lithium concentrations and achieve individualized medication for clinical safety. The dosage range of lithium carbonate was 500-1,500 mg/day, with a target blood lithium concentration of 0.4-0.8 mmol/L for maintenance treatment and a range of 0.6-1.2 mmol/L for acute treatment, aiming to minimize the occurrence of lithium toxicity. In addition to lithium carbonate, patients in the HG received antihypertensive medications, including calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEI), and angiotensin II receptor blockers (ARB), as prescribed by internal medicine physicians.

Patient blood lithium concentration

Both groups of patients followed medication instructions and received drug treatment for at least one month. Blood samples were collected when the patients reached steady-state blood lithium concentrations. Patients were required to fast for 8 h prior to blood collection. A total of 5 mL of blood sample was collected and mixed with anticoagulants such as ethylene diaminetetraacetic acid (EDTA) to prevent blood coagulation. The collected blood samples were centrifuged at 3,000 rpm for 3 min, and the upper layer of serum was collected. According to the instructions, the serum was mixed with an

extraction reagent, and methanol was used to remove protein interference. The samples were then injected into a high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) system using an autosampler. Appropriate chromatographic and mass spectrometry conditions were set, and the analysis was performed by running the program and reading the results.

Comparison of concentration to dose ratio (C/D) of lithium carbonate in patients

The C/D value of blood lithium refers to the ratio between the blood lithium concentration and the administered dose. The C/D value reflects the metabolic status of the drug in the body, where a higher C/D value indicates slower metabolism of lithium carbonate. The administered dose was recorded for each patient, and blood lithium concentrations were monitored at multiple sampling points. The blood lithium concentration at each measurement time point was calculated in relation to the corresponding dose administered.

The effect of different antihypertensive drugs on C/D value

Considering that lithium carbonate is primarily metabolized through renal pathways, different antihypertensive medications may have an influence on the C/D value of blood lithium. Baseline data of hypertensive patients, including the types and administration of antihypertensive drugs, as well as blood lithium concentrations and C/D values, were recorded and compiled in software for data collection and statistical analysis.

Young mania rating scale (YMRS)

The YMRS, developed by Yang *et al.* in 1978, encompasses 11 items related to thinking, language, sleep, and other aspects. A higher score indicates more severe symptoms, and it is commonly adopted in clinical practice to assess the symptoms and severity of mania in patients. The scale was administered by a physician through face-to-face interviews or observations of the patient, and scores were assigned to each item and recorded by summing up the individual item scores.

Comparison of adverse reactions (ARs)

ARs such as nausea, vomiting, dry mouth, constipation, dizziness, and insomnia occurring during the treatment process were tracked and documented. The number of cases experiencing these ARs was recorded and analyzed for further analysis.

Statistical analysis

Using SPSS 22.0, normally distributed continuous

data were denoted as mean $\pm$ standard deviation, and the t-test was adopted for statistical analysis. Categorical data were presented as cases (%) and analyzed using the chi-square test. $P < 0.05$ was statistically significant for detecting differences between groups.

RESULTS

In the CG, the average medication dosage was 0.84 ± 0.47 g/d, and the average blood lithium concentration was 0.78 ± 0.27 mmol/L. In the HG, the average medication dosage was 0.92 ± 0.32 g/d, and the average blood lithium concentration was 0.89 ± 0.20 mmol/L. Based on the results analysis, the HG had a markedly superior average blood lithium concentration to the CG ($P < 0.05$) (Fig. 1).

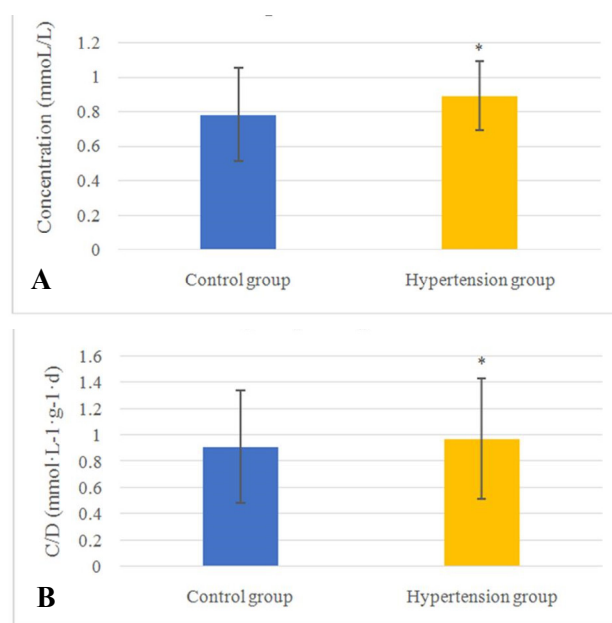


Fig. 1. Effect of hypertension on blood lithium concentration (A), and lithium concentration to dose (C/D) ratios (B) of manic episode patients.

Based on the records of patients' lithium carbonate dosage and blood lithium concentrations, the average blood lithium C/D in the CG was 0.91 ± 0.43 mmol·L⁻¹·g⁻¹·d, while in the HG, it was 0.97 ± 0.46 mmol·L⁻¹·g⁻¹·d. The HG had a greatly higher blood lithium C/D ratio versus the CG ($P < 0.05$) (Fig. 2). Further subgroup analysis based on the antihypertensive medications used revealed the results for the ACEI group, ARB group, and CCB group (Fig. 3). The blood lithium C/D ratio differed slightly in the ACEI and ARB groups relative to the CG ($P > 0.05$). Nevertheless, the CCB group showed an increase in the blood lithium C/D ratio versus the CG ($P < 0.05$).

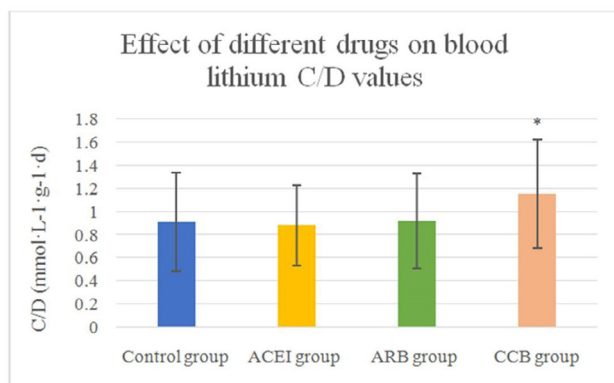


Fig. 2. Effect of different drugs on the blood lithium concentration to dose (C/D) ratios.

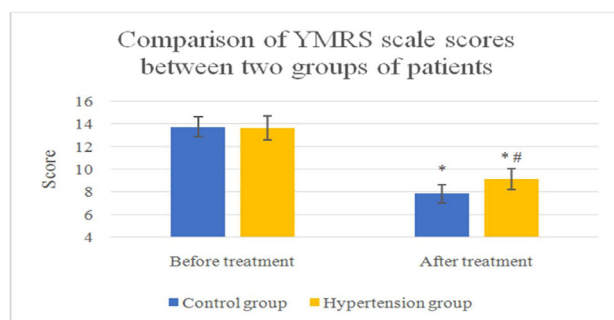


Fig. 3. Effect of hypertension on young mania rating scale (YMRS) scores of manic episode.

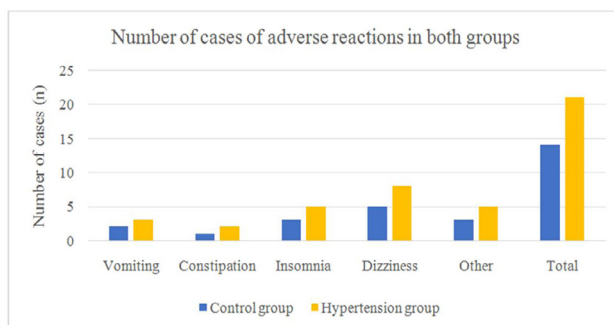


Fig. 4. Effect of hypertension on different adverse reactions (ARs) in manic episode patients.

The YMRS scores differed inconsiderably between the CG and the HG before treatment ($P>0.05$). After treatment, both groups showed a drastic reduction in YMRS scores (Fig. 4). The results indicate that after treatment, the average YMRS score in the CG was 7.84 ± 0.82 , while in the HG, it was 9.12 ± 0.89 . The YMRS score in the HG was superior to the CG ($P<0.05$).

The results of ARs in the both groups are summarized

in Figure 4. The results indicate that the number of patients experiencing ARs such as vomiting, constipation, and dizziness was higher in the HG compared to the CG. Furthermore, the total number of patients experiencing ARs in the HG was markedly superior to that in the CG ($P<0.05$). Specifically, the occurrence of ARs in the both groups was predominantly concentrated within 3 to 15 days. Within the first 3 days, the proportion of patients experiencing ARs was 20.0%, while after 15 days, the proportion increased to 31.4% (Table I).

DISCUSSION

Mania is a severe mood disorder, and lithium salts are commonly utilized as therapeutic agents. The discovery of lithium carbonate as a psychotropic medication was initially incidental, as it was originally used for the treatment of cardiovascular diseases. Lithium ions have extensive physiological functions in the human body. They not only improve the sodium ion exchange between neuronal cell membranes by affecting adenosine triphosphatase, thereby reducing synaptic norepinephrine concentrations and exerting anti-manic effects, but also act on the nervous system through the regulation of basal protein kinase C levels and G-protein expression (Elboga *et al.*, 2017; Shadhin *et al.*, 2020). Currently, lithium carbonate has been clinically proven to be effective and widely adopted in the treatment and prevention of manic episodes. Nevertheless, lithium carbonate has a low safety index and a narrow range of use (Tabibzadeh *et al.*, 2021; Zhang *et al.*, 2022). It is recommended that patients who require long-term lithium carbonate treatment maintain their blood lithium concentration between 0.5 to 0.8 mmol/L to ensure medication safety. Acute lithium therapy patients may reach up to 1.2 mmol/L. When lithium carbonate is utilized as a therapeutic approach, monitoring the patient's blood lithium concentration becomes crucial, and therapeutic drug monitoring has become an integral part of standard lithium carbonate therapy. When the blood lithium concentration is ≥ 1.50 mmol/L, the likelihood of experiencing severe ARs significantly increases, leading to damage to the nervous system, endocrine system, cardiovascular system, and symptoms such as dizziness, impaired consciousness, nausea, vomiting, and dry mouth (Nilsson *et al.*, 2021).

The metabolism of lithium is influenced by various factors, not only changes in renal function, but also the interference of other factors such as antihypertensive drugs, nonsteroidal anti-inflammatory drugs, which can affect the excretion and reabsorption of lithium, thereby influencing blood lithium concentration (Dornebal *et al.*, 2019; Mehandru *et al.*, 2022; Zhang *et al.*, 2022). With

the economic growth in our country, the population with hypertension is increasing. Some studies suggest that there may be overlapping pathophysiological mechanisms between hypertension and manic episodes. Nevertheless, research in this area is still limited, and further exploration is needed to gain a better understanding.

Hypertension may have multifaceted effects on patients with manic episodes. Studies have shown that hypertensive patients often exhibit cardiovascular dysfunction and vascular tension, which can potentially influence blood circulation as well as the absorption, distribution, and elimination of medications. Common comorbid factors in hypertensive and manic patients may also interact with each other (Deotale *et al.*, 2022; Gimenez-Palomo *et al.*, 2022). For instance, cardiovascular diseases, metabolic syndrome, and obesity, closely associated with hypertension, may be more prevalent among individuals with mania. These comorbid factors could be associated with the occurrence and severity of manic episodes and can impact treatment response (Basile *et al.*, 2014; Liu *et al.*, 2022). Moreover, some commonly applied antihypertensive medications may interfere with neural regulation and metabolic processes in individuals with mania, leading to exacerbation of manic symptoms or difficulties in their control (Colbourne *et al.*, 2021; Yasui-Furukori and Fujii, 2013). In the CG, the average blood lithium concentration was 0.78 ± 0.27 mmol/L, while in the HG, it was 0.89 ± 0.20 mmol/L. The HG exhibited a substantially higher average blood lithium concentration versus the CG ($P < 0.05$). In terms of lithium C/D, the CG had an average C/D value of 0.91 ± 0.43 mmol·L⁻¹·g⁻¹·d, while the HG had an average C/D value of 0.97 ± 0.46 mmol·L⁻¹·g⁻¹·d. The HG had a dramatically higher average C/D value than the CG ($P < 0.05$). These findings suggest that hypertension may further impact blood lithium concentration due to alterations in lithium metabolism among patients with manic episodes. When hypertension patients were grouped based on the antihypertensive medications used, no marked differences were found in average C/D values among the ACEI group, ARB group, and the CG ($P > 0.05$). Nevertheless, the CCB group showed a higher average C/D value than the CG ($P < 0.05$). This finding differs slightly from some previous studies, which may be attributed to variations in specific antihypertensive drug categories and individual patient factors. Further in-depth research is still warranted to explore these differences.

Lithium carbonate can reduce the sensitivity of adrenergic and dopamine receptors, enhance acetylcholine function, and lead to a series of neurological impairments such as seizure-like episodes and impaired consciousness (Aggarwal *et al.*, 2022). Hypertensive patients often

require long-term use of antihypertensive medications, some of which may cause a range of ARs such as dizziness, hypotension, and cardiac arrhythmias. The combined use of multiple antihypertensive drugs with lithium carbonate increases the risk of ARs (Kumar *et al.*, 2022). The results showed that the average YMRS score of the HG after treatment was 9.12 ± 0.89 , notably higher than that of the CG ($P < 0.05$), indicating that the HG exhibited poorer outcomes after treatment relative to the CG. Further analysis of ARs in the both groups revealed that the total number of patients experiencing ARs in the HG was superior to the CG ($P < 0.05$), with a higher number of cases of vomiting, constipation, and dizziness observed in the HG. The occurrence of ARs in both groups was concentrated within the first 3-15 days, accounting for 48.6% of the total ARs. In short, special attention should be given to the condition of hypertensive patients with manic episodes within the first 3-15 days of treatment to further ensure the effectiveness and safety of medication therapy.

CONCLUSION

High blood pressure had a significant impact on blood lithium concentration and its C/D in patients with manic episodes, suggesting that high blood pressure may lead to a slowing of lithium metabolism. Hence, close monitoring of blood lithium concentration is necessary in hypertensive patients undergoing lithium carbonate treatment to avoid toxicity associated with high concentrations. Additionally, attention should be paid to the occurrence of ARs. Further research is needed to investigate the mechanisms underlying the effects of high blood pressure on blood lithium in patients with manic episodes, in order to optimize treatment strategies and ensure patient safety.

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IRB approval

This study was approved by the Wuhan Wudong Hospital, Wuhan 430084, Hubei Province, China.

Ethical approval

The study was carried out in compliance with guidelines issued by ethical review board committee of

Wuhan Wudong Hospital, China. The official letter would be available on fair request to corresponding author.

Statement of conflict of interest

The authors have declared no conflict of interest.

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