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Research Paper

Research progress on biological effects of lithium carbonate

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ABSTRACT: *With the development of society and the progress of science and technology, lithium containing elements and compounds have been widely used in people's life.Lithium can regulate the central nervous system and protect the biofilm. It can also improve the hematopoietic function and improve the human immune function.Lithium is widely found in the human body and is being studied as an essential element.Lithium carbonate is one of the most commonly used lithium drugs. It is an effective tranquilizer, which can make brain cells more active and suppress abnormal mood, and is used to treat mental illness.In recent years, new uses of lithium have emerged in the treatment of viral diseases, skin pathogens, cancer and AIDS, playing a role in viral replication, cytokines, cell signaling, cell regulation and immune response.*

KEY WORDS: *Lithium carbonate; Inorganic drugs; Bipolar disorder; Toxicity; Biological effect*
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I. INTRODUCTION

Lithium was discovered in 1817 by Johann Arfvedson, a Swedish scientist, when he analyzed perlithium-feldspar. His teacher Jons Jakob Berzelius named it lithium[1]. However, it was not until 1855 that Bensen and Marcheson adopted the method of electrolyzing and melting lithium chloride that metal elements were produced.In recent years, with the development of society and the progress of science and technology, lithium metal is widely used in the production of light metal alloy, becoming the fourth generation of high-tech metal after iron, aluminum, titanium;Lithium salts are widely used in the production of glass, lubricants, batteries and medicines, and have rare clinical pharmacological and biochemical properties when used as medicines.

Lithium compounds have been used as medicines for more than 140 years.Lithium urate was first used as a treatment for "gout and rheumatism" and later as a treatment for various disorders by adding small doses of lithium bromide to mineral water[2].In 1949, the Australian psychiatrist Cade discovered its clinical value in the treatment of psychiatry, making lithium the first modern drug for the treatment of psychiatry[3].In the late 1940s, Cade injected himself with lithium carbonate and lithium citrate to test whether the lithium preparations were toxic to humans, and the results passed without incident.In addition, I organized 10 mental patients to participate in the clinical trial in the hospital where I worked. All patients were injected with lithium carbonate, and most of the mental patients' symptoms were relieved. This result caused a sensation in the international medical community and was also the first therapeutic drug that can effectively control mental illness discovered in the medical community[4].Since then, in the past 60 years, although pharmacologists have developed many kinds of psychotic drugs, lithium carbonate has always been the first choice for the treatment of manic psychosis, and is also one of the classic psychotic drugs included in the world pharmacopoeia[5].

There has not been an effective drug to treat any serious mental illness, and this is the first time a lithium drug has been shown to be effective in treating mania.However, when lithium chloride was used as a substitute for sodium chloride in the treatment of hypertension, it resulted in the death of four patients with cardiovascular disease.

Garrod and Johnson chronicle the "toxic panic."This incident led the US Food and Drug Administration to restrict the use of lithium as a psychiatric drug for 15 years.But because of its unique therapeutic benefits, European countries have argued that selective use of lithium is better than banning it, arguing that it needs to be used within safe and effective limits.In the 1950s Schouw and others found that lithium was safe to use for bipolar disorder when the dosage of lithium was lower than that of CADE[6].The benefit of lithium in treating psychosis is to reduce suicidal and aggressive behavior, as well as aggressive behavior.In the hands of experienced doctors, it can reduce or eliminate periodic mood swings, improve patients' quality of life, and

improve many people who would otherwise be suicidal.

II. CLINICAL APPLICATION OF LITHIUM CARBONATE

2.1 Evaluation of clinical efficacy of lithium drugs

Lithium drugs are usually given orally as lithium carbonate tablets[7] and are currently mainly used to control manic episodes of bipolar disorder.The total dose was 30 mmol (2 g) per day at the highest dose[8].Lithium has a narrow therapeutic index. Muller-Oerlinghausen studied that the number of suicides in patients who responded to lithium drug treatment was significantly reduced, and the use of lithium drug was superior to other drugs in reducing suicidal tendency and mortality, while other drugs only helped stabilize mood[9-11].Bipolar disorder is a psychiatric diseases, is a kind of characterized by abnormal emotion is high or low mood disorder, at the same time accompanied by periodic episodes of mania and depression, may be present in patients with the same two intermittent alternant recurrent symptoms, can also be a symptom is given priority to break out repeatedly, in patients with mental activity can be shown as perfectly normal off-season[12].With the increase of work pressure, the incidence of bipolar disorder is on the rise and tends to be younger, bringing a huge burden to the society and family[13].Studies of twins and adopted children have shown that the disease is inherited;Women are twice as affected as men, and the incidence increases after menopause.Patients with recurrent affective disorder tend to have higher socioeconomic backgrounds, have marital problems or are unmarried.Due to disease damage, suicide is the main cause of death in severe depression stage[14].

2.2 Side effects and toxicity of lithium drugs

Lithium carbonate, as a mood stabilizer, is often used in the treatment of emotional disorders. Lithium-ion can enhance the effect of 5-hydroxytryptamine (5-HT) and inhibit the β-receptor-adenylate cyclase system.The treatment amount of lithium carbonate is close to the poisoning amount, serious poisoning is rare, the dosage should be strictly controlled when using lithium drug treatment, when the blood lithium concentration is more than 1.4mmol/L, patients will appear lithium poisoning symptoms[15].More serious poisoning symptoms include hand tremors, dizziness, drowsiness, diarrhea, slurred speech and vomiting due to high doses or other physiological or pharmacological changes resulting in fluid balance disorders[16].In addition, long-term lithium treatment patients are also prone to renal damage and polyuria, high dose of lithium is not suitable for long-term treatment of mania patients. Moreover, precursory symptoms or early poisoning symptoms of lithium poisoning do not appear independently, and there is no clear dividing line between adverse reactions and poisoning. Therefore, the monitoring of lithium drug concentration is conducive to the regulation of treatment and maintenance dose, and the timely detection of poisoning symptoms[17].

As early as 1881 Garrod described some of the side effects of lithium: "Prolong use of the drug seems to affect the nervous system, such as the shaking or trembling of the hand."Mild tremor, sometimes present at low doses, may be the reason for the lowest dose or the addition of a blocker. Side effects usually occur within 4 hours.Long-term side effects include aggravation of skin disease, weight gain, leukocytosis, hypothyroidism, etc., so special attention should be paid to long-term use of lithium carbonate may lead to chronic lithium poisoning[18].

2.3 Drug interactions

Combination therapy initially requires reducing the dose of two drugs and reducing the incidence of toxic side effects.Interaction between lithium and certain diuretics and resistant drugs.Thiazide diuretics increase serum lithium concentration and enhance lithium reabsorption[19]; Carbonic anhydrase inhibitors and xanthine derivatives that reduce serum lithium concentration by increasing renal lithium excretion.Low dose propranolol, β-blocker can treat hand tremor caused by lithium poisoning.Some interactions between lithium and other drugs can be beneficial.In approximately 60% of patients with depression, conventional treatment fails, and a combination of lithium and antidepressants or anticonvulsants has successfully cured some of the more refractory affective disorders [20].

2.4 Pharmacokinetics of lithium carbonate

Lithium carbonate drugs are successful in the treatment of psychosis, and patients need to regularly monitor and analyze the fluctuation of serum lithium concentration within a safe range, so as to provide reference for rational clinical use[21].In this study, oral administration of lithium carbonate tablets at a daily dose of 21 millimol (equivalent to 800 mg of lithium carbonate) was performed. 5-10 ml of venous blood was collected before the elbow, and the concentration of lithium in blood was determined by atomic absorption spectrometry (AAS) or flame emission spectrometry (FES).The results showed that the oral dosage of lithium reached 0.2 mmol/L for 4 hours, and then gradually decreased, and the half-life of urinary excretion was about 24 hours.Lithium is completely excreted by the kidneys and 95% of the absorbed dose can be recovered in the urine.The curve of average plasma lithium concentration over time was shown in Figure 1.

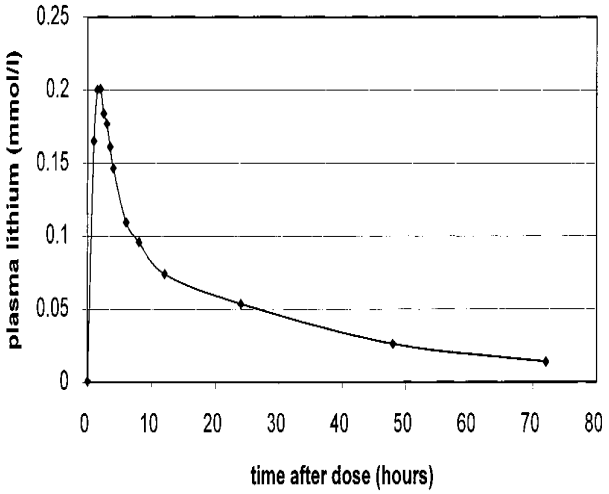

Fig. 1 Curve of mean plasma lithium concentration over time

III. LITHIUM IS DISTRIBUTED IN THE BODY AND CELLS

With the wide application of lithium and lithium salts, lithium is gradually enriched in food, drinking water and medicine, and then enters the biological body. As a specious trace element necessary for life, it has attracted the attention of scientists.Therefore, it is very necessary to study the biological effect of lithium.So the first thing we need to figure out is how lithium is distributed in the body and in cells.Thellier, Davenport and Schou injected lithium drugs intravenously into experimental animals and mapped the distribution of lithium in different regions of the whole body and brain by using micro-localization techniques through neutron activation experiments[22].The technique involves irradiating a stable isotope of 6Li in an atomic reactor with neutrons. The 6Li nucleus absorbs a neutron and the nucleus immediately fission to produce an alpha particle and an isotope of 3H, creating a suitable detector that tracks the changes in the tissue containing 6Li.To investigate the probability of lithium in rat and mouse brain tissue, embryo and mutant myelin formation disorders.The results showed that the concentration of lithium in brain and endocrine gland was higher than that in other tissues.Lithium is a small moving ion, and its distribution in living cells is difficult to define[23].

If the plasma concentration of lithium is 1 mmol/L, the concentration of lithium in the renal papilla may reach 60-65 mmol/L with relative water loss.Similarly, local concentrations of cellular fluid flowing through the gastrointestinal tract during the absorption of lithium carbonate tablets may be very high.Eichner and Opitz also demonstrated sex differences in normal lithium levels in the adrenal glands and thymus.The distribution of lithium in rats was shown in Figure 2. The drug was given at the rate of 1 mmol/kg per day according to body weight, and the average value of lithium concentration 6 hours after drug withdrawal.

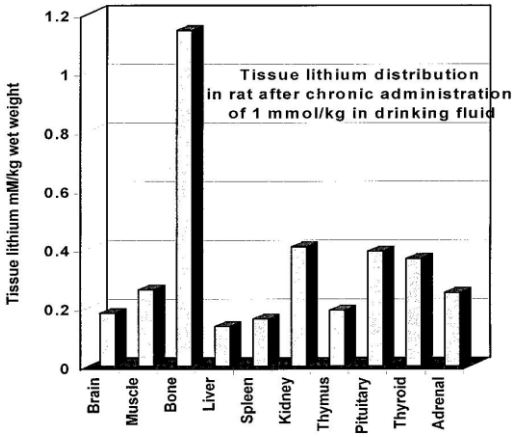

Fig. 2 The average value of lithium concentration after 6h of drug withdrawal after 1 mmol/kg of body weight was given

Lithium drugs are usually administered orally, digested in the stomach, absorbed in the intestine and ileum, and the physiological control is exerted by the mucosal layer of the intestine. Mucosal epithelial cells are formed by connective tissue and desmosomes embedded in the underlying layer.All epithelial cells have this structure, and the space between these cells may be a barrier that penetrates through the membrane.Studies have shown

that lithium enters cells through membrane transmembrane transport behavior[24-25], namely: potassium pump, sodium-potassium cooperative transport, sodium-lithium exchange and other pathways.

IV. MECHANISM OF ACTION OF LITHIUM

Due to the "diagonal relationship" between lithium and magnesium[26], lithium competes with magnesium and calcium at their biogand binding sites, and lithium intake can affect magnesium metabolism.Magnesium is one of the essential life trace elements. It has a very important function in human tissues. It is an activator of more than 300 enzymes, participates in carbohydrate, fat and protein metabolism, and plays an important role in energy transfer, storage and utilization.Its main function is as an activator of bisphosphonate transfer reactions, including hydrolysis and transfer of organic phosphate groups, involving ATP.Studies have shown that lithium also binds to adenosine diphosphate. Although lithium and magnesium have many different cellular functions, their activity can be controlled by a relatively simple osmotic relationship, which can affect metabolism if lithium competes for magnesium-dependent enzyme sites.High concentrations of lithium also inhibit polysaccharide enzymes, and "lithium therapy" has been shown to modify partial magnesium metabolism: magnesium in serum and in urinary excretion increases as lithium ions increase.

V. THE HERITABILITY OF LITHIUM AND ITS POTENTIAL TO BECOME AN ESSENTIAL ELEMENT FOR LIFE

Patt et al. investigated the possibility of lithium becoming an essential element in mice and fed three generations of animals on a lithium-free diet.The first-generation pituitary gland has more than 10 times more lithium than any other tissue except the adrenal gland (the adrenal gland has about half the total lithium of the pituitary gland).Lithium was found in the pituitary gland and adrenal gland of the lithium-free and commercial-fed groups. Lithium was highest in the bones of the control group, which could be considered an indicator of excess lithium, the latter being consistent with the bone findings.In the lithium-free animals of the second generation, lithium levels in the pituitary gland were the same as in the lithium-free animals of the first generation and the control group, and lithium levels in the adrenal gland were slightly reduced, but still higher than in the rest of the other tissues.These results indicate that the pituitary gland and adrenal gland accumulate lithium and ensure that they are not deficient in lithium, and female animals of the second and third generations have reduced fertility compared to the first generation and normal control group, but their growth rate is not affected[27].

In another experiment, animals were weaned on either a low-lithium diet (0.005 to 0.015 PPM) or a diet with a "normal" lithium content.Through the analysis of the experimental group of the third generation, the results are consistent with the experimental results of lithium containing drugs.However, lithium accumulates to a significant extent in bones and teeth, and to a lesser extent in the anterior pituitary and adrenal glands.Due to dietary restrictions, lithium concentrations remained about the same in both endocrine organs for three generations, while lithium levels continued to decline in all other organs.Lack of lithium reduced fertility in the second - and third-generation female mice, but had no significant effect on the growth rate of young mice.

VI. PROSPECTS AND PROSPECTS

In recent years, new uses of lithium are shown in the treatment of viral diseases, skin pathogens, cancer and AIDS, and play roles in viral replication, cytokines, cell signaling, cell regulation and immune response. For example, the use of lithium is beneficial for patients with immunodeficiency to receive zidovudine antiviral therapy;High concentration of lithium about 40 mmol/L can inhibit the automatic replication of herpes, chickenpox, adenovirus, lithium drugs in the treatment of skin diseases, can reduce the virus secretion of endotoxin, so as to quickly treat herpes ulcer.Lithium compounds have also been found to be promising in the treatment of autoimmune diseases and systemic lupus erythematosus.

REFERENCES

[1]. Yang Y, Ren C J，Zhang R Z, et al.Evaluation of clinical effect and safety of quetiapine combined with lithium for the treatment of bipolar mania.Practical Journal of Clinical Medicine, 2016,13(1): 35–37.
[2]. Deng S R.Trace element Li and health of human body.Guangdong Trace Elements Science,2000,7(11): 12–14.
[3]. Kong L C，Kong X R. Lithium - a good medicine for mental illness. Metal world，2001,1: 9.
[4]. Bao S, Zhuang H Y, Liu S S, et al.The effect of home intervention assisted lithium carbonate in the treatment of bipolar disorder in convalescent period.China Journal of Hospital Pharmacy,2020,40(01):125-126.
[5]. Chris O, Michael J A.Medicinal Inorganic Chemistry: Introduction . Chem. Rev.1999,99（9）: 2201-2204.
[6]. Kong G Q,Guo W. Current situation and progress of lithium carbonate.Chinese Journal of Clinical Pharmacy;Chin J Clin Pharm，2009,18(3): 183–185.
[7]. Sun J. Tablets of magnesium valproate and lithium carbonate sustained-release tablets in the treatment of manic episodes of bipolar disorder in patients with clinical efficacy. Medicine and Clinical Practice, 2016, 2: 51–53.
[8]. Janusz K R. Response to lithium in bipolar disorder: Clinical and genetic findings. ACS Chem.Neurosci, 2014, 5 (6): 413–421.
[9]. Emanuel S, Sudhakaran P, Phil W, et al. High Throughput Lipidomic Profiling of Schizophrenia and Bipolar Disorder Brain Tissue

Reveals Alterations of Free Fatty Acids, Phosphatidylcholines, and Ceramides. Proteome Res, 2008, 7 (10): 4266–4277.
[10]. Stanley I R. Lithium and the Other Mood Stabilizers Effective in Bipolar Disorder Target the Rat Brain Arachidonic Acid Cascade . ACS Chem.Neurosci, 2014, 5 (6): 459–467.
[11]. Yuan S, John R, Bao L L, et al. Lithium,a Common Drug for Bipolar Disorder Treatment, Regulates Amyloid-β Precursor Protein Processing. Biochemistry, 2004, 43 (22): 6899–6908.
[12]. Sun J Z.Advances in the determination of lithium.Physical and Chemical Examination (Chemical Volume),2009,45(10): 12401–244.
[13]. Nassar A , Azab A N. Effects of Lithium on Inflammation . ACS Chem. Neurosci, 2014, 5 (6): 451–458.
[14]. Yang Y，Ren C J，Zhang R Z,et al. Evaluation of clinical effect and safety of quetiapine combined with lithium for the treatment of bipolar mania. Practical Journal of Clinical Medicine，2016,13(1): 35–37.
[15]. Xiong H. Comparison of dialectical classification of Chinese and western medicine in treatment of mania. Electronic Journal of Clinical Medical Literature,2018,5(56):33.
[16]. Zhang D L, Chen L, Yao P. One case of lithium poisoning caused by combined use of diclofenac sodium and lithium carbonate. China Licensed Pharmacist, 2014,11(7): 54–56.
[17]. Hao Y M,Han Y Y. Application of thiazide diuretics in patients with hypertension.Clinical Medication Journal,2012,10(1): 4–7.
[18]. Pang S Z. Clinical efficacy of risperidone combined with lithium carbonate in patients with acute mania.Chinese Journal of Minkang Medicine,2019,31(17):74-75+89.
[19]. Ling Y L.Chronic lithium poisoning caused by long-term use of lithium carbonate.Journal of Adverse Drug Reactions,2009,11(3): 187–196.
[20]. Li A J, Shi L. Monitoring of serum lithium concentration in patients with mental illness and analysis of its influencing factors. China Practical Medicine,2010,5(6): 90–91.
[21]. Davie, R.J. In Lithium and the cell. Academic Press,1991, Chapter 13: 243-248.
[22]. Zakir Hossain S M, Luckham R E, McFadden M J, et al. Reagentless Bidirectional Lateral Flow Bioactive Paper Sensors for Detection of Pesticides in Beverage and Food Samples. Anal. Chem, 2009, 81 (21): 9055–9064.
[23]. Niu Y H,Zou Y Z,Wang X F. Screening the stress sensitive sites of angiotensin Ⅱ type I receptor. Chinese Journal of Pathophysiology,2009,25(3): 427–431.
[24]. Jin Y G , Xin R, Tong L,et al. Combination Anti-HIV Therapy with the Self-Assemblies of an Asymmetric Bolaamphiphilic Zidovudine/Didanosine Prodrug . Mol. Pharmaceutics, 2011, 8 (3): 867–876.
[25]. Kawamura A, Abrell L M, Maggiali F, et al. Biological Implication of Conformational Flexibility in Ouabain:Observations with Two Ouabain Phosphate Isomers. Biochemistry, 2001, 40 (19): 5835–5844.
[26]. Wu B L, Gu X N,Zhan J M, et al.Recent progress of determination of lithium and its compounds. Guangdong Chemical Industry, 2015,42（295）: 65–73.