นิพนธ์ต้นฉบับ • Original Article

ความชุกและปัจจัยเสี่ยงในการเกิดพิษของลิเทียม ณ โรงพยาบาลศรีนครินทร์

วรรณวิไล เลาลัคนา[1], เบญจมาศ วรรณวิเชษฐ์[2]
[1]คณะเภสัชศาสตร์
[2]หน่วยบริการข้อมูลยา งานเภสัชกรรม โรงพยาบาลศรีนครินทร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น อ.เมือง จ.ขอนแก่น

Prevalence and Risk Factors of Lithium Toxicity at Srinagarind Hospital

Wanwilai Laolakkana[1], Benjamas Wannawitchate[2]
[1]Faculty of Pharmaceutical Sciences
[2]Drug information center, Pharmacy service division, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Muang, Khon Kaen 40002, Thailand

หลักการและเหตุผล: ลิเทียมเป็นยาที่มีการใช้บ่อยในการรักษาโรคอารมณ์สองขั้ว โดยลิเทียมจัดเป็นยาที่มีช่วงการรักษาแคบเพราะฉะนั้นจึงมีโอกาสในการเกิดภาวะแทรกซ้อนจากการใช้ยาในระยะยาว
วัตถุประสงค์: เพื่อหาความชุกและปัจจัยเสี่ยงในการเกิดพิษของลิเทียมในผู้ป่วยที่ รพ.ศรีนครินทร์ จ.ขอนแก่น
รูปแบบการศึกษา: เป็นการศึกษาเชิงพรรณาแบบเก็บข้อมูลย้อนหลัง ในผู้ป่วยที่ได้รับยาลิเทียมระหว่างวันที่ 1 มกราคม พ.ศ. 2546 ถึง 31 พฤษภาคม พ.ศ. 2549
ผลการศึกษา: จากการศึกษาในผู้ป่วยจำนวน 273 ราย คิดเป็น 308 ครั้ง พบว่ามีผู้ป่วยที่เกิดพิษจากลิเทียม 65 ครั้ง (ร้อยละ 21.10) โดยแบ่งเป็นผู้ป่วยใน 12 ครั้ง (ร้อยละ 3.90 ของทั้งหมด) และผู้ป่วยนอก 53 ครั้ง (ร้อยละ 17.21 ของทั้งหมด) ความชุกของอุบัติการณ์เกิดพิษในปี 2546 ถึง 2548 คือ ร้อยละ 19.1, 20.3 และ 31.7 ตามลำดับ ซึ่งสามารถแบ่งระดับความรุนแรงของการเกิดพิษได้เป็นระดับอ่อน 42 ครั้ง (ร้อยละ 64.62) ระดับปานกลาง 20 ครั้ง (ร้อยละ 30.80) และระดับรุนแรง 3 ครั้ง (ร้อยละ 4.62) สำหรับปัจจัยที่เพิ่มความเสี่ยงในการเกิดพิษจากลิเทียม ได้แก่ ขนาดยาลิเทียม 900-1200 มิลลิกรัม (OR: 2.2; 95% CI 1.2 to 4.2) ขนาดยามากกว่า 1,200 มิลลิกรัม (OR: 5.4; 95% CI 1.8 to 16.6) ผู้ป่วยโรคจิตเภท (OR: 3.3; 95% CI 1.1 to 10.1) และผู้ป่วยที่ได้รับยากลุ่ม SSRIs (OR: 2.8; 95% CI 1.3 to 6.1)

Background: Lithium is commonly used in the treatment of bipolar disorder. Lithium has narrow therapeutic range; its toxicity therefore is also a frequent complication of chronic lithium therapy.
Objective: The purposes of this study were to determine the prevalence and risk factors of lithium toxicity in Thai patients at Srinagarind Hospital in Khon Kaen.
Methods: This descriptive retrospective study was performed by reviewing the OPD cards and medical records of patients who had received lithium during the period from 1 January 2003 to 31 May 2006.
Results: There were 273 patients (308 visits) who had relevant OPD card and medical records. 65 patients had lithium toxicity of which 12 (3.9%) were from IPD and 53 (17.2%) were from OPD. The prevalence per year was 14.1% in 2003, 20.2% in 2004 and 31.7% in 2005. Lithium toxicity was classified as mild (42 reports, 64.4%), moderate (20 reports, 30.8%) and severe (3 reports, 4.6%), respectively. Risk factors for lithium toxicity were a dose of 900-1200 mg (OR: 2.2; 95% CI 1.2 to 4.2), a dose more than 1200 mg (OR: 5.4; 95% CI 1.8 to 16.6), patients with schizophrenia (OR: 3.3; 95% CI 1.1 to 10.1) and patients who received SSRIs drugs (OR: 2.8; 95% CI 1.3 to 6.1).
Conclusion: The finding of this study supports that the use of lithium for treatment of bipolar disorder should be

สรุปผลการศึกษา: การใช้ลิเทียมในการรักษาโรคอารมณ์สองขั้ว ควรมีการเฝ้าระวังและติดตามอย่างใกล้ชิดสำหรับผู้ที่มีโอกาสเกิดพิษ ได้แก่ ผู้ป่วยที่มีการใช้ยาขนาด 900 มิลลิกรัมขึ้นไป ผู้ป่วยจิตเภทและผู้ป่วยที่ได้รับยากลุ่ม SSRIs close monitored especially in the patients who receive a dose of more than 900 mg, especially patients with schizophrenia and patients who received SSRIs drugs.

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Introduction

Lithium is commonly used in the treatment of depressive and bipolar disorders. Lithium is also effective in the prophylaxis of bipolar disorder relapse. The initial treatment dose is 600-900 mg/day, and the average maintenance dosage range is usually 450-1,200 mg/day to a level of 0.8-1.2 mEq/L. Lithium is minimally protein bound and has an apparent volume of distribution of 0.6 L/kg. The plasma elimination half-life of a single dose of lithium is from 12-27 hours. The half-life increases to approximately 36 hours in elderly patients and may be considerably longer with chronic lithium therapy.[1-3] Lithium has a narrow therapeutic index (0.6-1.2 mEq/L)[4] and lithium intoxication is a frequent complication of long term therapy. Mild toxic reactions occur at lithium levels of 1.5 to 2 mEq/L such as nausea, diarrhoea, blurred vision, polyuria, fine resting tremor, muscular weakness and drowsiness. Moderate reactions occur at levels of 2 to 2.5 mEq/L such as increasing confusion, nystagmus, ataxia, myoclonic twitches, increased deep tendon and jerks and urinary or faecal incontinence. Severe reactions occur at lithium levels exceed 2.5 mEq/L such as coma, convulsions, cerebellar signs, hypotension and renal failure.[5-7] There are many factors that can affect an individual patient's serum lithium level. The clearance might increase during manic episodes, which would decrease serum lithium concentrations. Another factor is changes in salt intake or diet, increased sweating, or a medical condition that causes fever or diarrhea. If fluid intake is insufficient, polyuria can lead to dehydration and possible toxic lithium levels.[1] Several medications are precipitating drugs for lithium toxicity such as thiazide diuretics, ACE inhibitors, anticonvulsants, calcium channel blockers, NSAIDs and SSRIs.[7-11]

Srinagarind Hospital of Khon Kaen University is a tertiary care center with 650 beds that serves the public of the northeast region of Thailand. There were an average of 170 patients who were on lithium therapy per year. The previous studies on lithium therapy were case reports and there are few studies on the prevalence and risk factors associated with lithium toxicity in Thai patients. The aims of this study were to determine the prevalence of the case and to evaluate the risk factors of lithium intoxication.

Methods

Setting and design

The descriptive retrospective study was done on the hospitalized patients and outpatients of Srinagarind Hospital of Khon Kaen University, Thailand by reviewing the OPD cards and medical records of the patients who had received lithium. This study was approved by The Khon Kaen University Ethics Committee for Human Research on August 21, 2006.

Study sample

The inclusion criteria were the patients who had received lithium during the period from January 2003 to 31 May 2006. The exclusion criteria were the patients who had received lithium less than 7 days and the patients whose OPD cards and medical records could not be retrieved.

Study procedure

The hospital number (HN) of patients who had received lithium was retrieved from the database of the Department of Pharmacy, Srinagarind Hospital. The pharmacist then retrieved the OPD cards and medical records to extract the information of demographic data, disease states, laboratory results, medication therapy, physical examination, lithium serum concentrations, sign/symptoms and treatment of lithium toxicity. The lithium concentrations were analyzed by atomic absorption spectroscopy. Other factors considered likely

to relate to the risk of developing lithium toxicity were recorded. The collected data were evaluated for toxicity and assessed causality with Naranjo's algorithm[12] by the pharmacist. The Naranjo's algorithm can be used to assess the likelihood that a change in clinical status is the result of an adverse drug reaction rather than the result of other factors such as progression of disease. The probability calculation of this algorithm divided likelihood to definite, probable, possible or doubtful. The toxicity was classified by the symptoms or lithium plasma concentration as mild (lithium level between 1.5 to 2.0 mEq/L), moderate (lithium level between 2.0 to 2.5 mEq/L) and severe (lithium level more than 2.5 mEq/L).

Statistical analysis

Descriptive statistics were used for patients' demographic data and comparison between the frequency and severity of toxicity of lithium for hospitalized patients and outpatient. The prevalence of lithium toxicity in patients was expressed as the percentage of the number of patients who had toxicity divided by the total number of patients who had received lithium per year. Association between the number of patients with toxicity and the patient's risk factors e.g. age, dose of lithium, lithium level more than 1.2 mEq/L, type of underlying diseases and type of concomitant medications were analyzed using Chi-square test and logistic regression.

Results

There were 273 patients (308 visits) who had relevant OPD cards and medical records. Sixty-three patients were hospitalized patients (IPD) and 245 were outpatients. Patients in this study were mostly aged less than 60 years (94.8%). The majority of patients were female (61.4%). The indications for lithium medication were bipolar disorder (48.4%), psychiatric disorder (29.6%) and hyperthyroidism (21.4%). The lithium dosages were 900-1,200 mg/day (55.5%), 300-600 mg/day (38.63%) and more than 1,200 mg/day (5.2%), respectively. In addition, the numbers of concomitant drugs were 1 to 5 items (68.8%) and 6 to 10 items (23.1%). Of the 308 visits, 65 (21.1%) patients had lithium toxicity of which 12 (3.9%) were in IPD and 53 (17.2%) were in OPD. The causality from Naranjo's algorithm was defined as possible in 67.7% and probable in 32.3%. Approximately, 64.6% of patients who had lithium toxicity were classified as mild, 30.8% moderate and 4.6% severe. The highest frequency of organ systems which were adversely affected by lithium were nervous system (70.7%, such as tremor, dizziness and extrapyramidal symptoms), gastrointestinal system (33.8%, such as nausea, vomiting and anorexia) and integumentary system (15.4%, such as erythema and alopecia), respectively (Table 1). According to the treatment data of lithium toxicity, the results indicated that 36.9% of patients were a decreased dose of lithium dose, 35.4% were discontinued lithium therapy and 7.7% were increased lithium interval. The prevalence of lithium toxicity in patients was presented in Figure 1. The study presented that the prevalence per year was 14.1% in 2003, 20.2% in 2004 and 31.7% in 2005. In 2006, the prevalence per year was 22.5% for which collected data for only the first five months was used in the analysis.

The findings in Table 2 showed that there were significant associations between lithium toxicity and the dosages, concomitant drug used and underlying disease. Using Chi-square test, patients who had experienced a dose of 900-1,200 mg/day and a dose more than 1,200 mg/day were significantly more likely to have toxicity (p=0.016 and p=0.002). However, no significant was found between a concentration of lithium more than 1.2 mEq/L (21 patients of which 8 pa tients (38.1%) detected toxicity) and lithium toxicity (p=0.768). Patients aged more than 60 years (9 patients of which 2 patients (22.2%) had lithium toxicity) also had no association risk with lithium toxicity (p=0.923). For using logistic regression,adjusted with total dose, butyrophenones, SSRIs, schizopherenia, anticonvulsants, and tricyclic antidepressants, the patients with schizophrenia were significantly more likely to have toxicity (OR: 3.3; 95% CI 1.1 to 10.1, p=0.033). Similarly, patients who received SSRIs drugs were significantly more likely to have toxicity (OR: 2.8; 95% CI 1.3 to 6.1, p=0.008).

Discussion

The result of this study showed that the number of patients with lithium toxicity was on average of 21.1% (65/308) and the highest prevalence was in the year 2005. As Figure 1 showed, the prevalence of lithium toxicity trend to increase each year. The prevalence in 2006 was less than in 2005 but the data were collected for the first five months

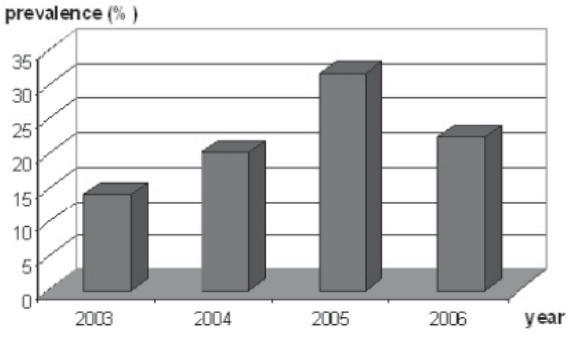

Figure 1 prevalence of lithium toxicity

only. The majority of patients who had lithium toxicity were classified as mild (64.6%) and the highest frequency of organ system which was adversely affected by lithium was the nervous system (70.7%). The associated risk factors for patients in this study were total dose per day, whereas schizopherenia and SSRIs concomitant therapy were also the associated risk factors according to the published data.[5,11] However, there were no significance was found with other concomitant drugs including NSAIDs, butyrophenones, anticonvulsants, tricyclic antidepressants and phenothiazine.

Table 1 Classification of lithium toxicity.

Characteristics	IPD (n=12)	OPD (n=53)	Total (n=65)
Lithium plasma level			
≤ 1.2 mEq/L	5 (41.7)	30 (56.6)	35 (53.9)
> 1.2 mEq/L	5 (41.7)	3 (5.7)	8 (12.3)
No data	2 (16.7)	20 (37.7)	22 (33.8)
Naranjo's algorithm			
Possible	8 (66.7)	13 (24.5)	21 (32.3)
Probable	4 (33.3)	40 (75.5)	44 (67.7)
Severity			
Mild	7 (58.9)	35 (66.0)	42 (64.6)
Moderate	3 (25.0)	17 (32.1)	20 (30.8)
Severe	2 (16.7)	1 (1.9)	3 (4.6)
Organ system			
Neurological	8 (66.7)	38 (71.7)	46 (70.7)
Gastrointestinal	6 (50.0)	16 (30.2)	22 (33.8)
Skin	0	10 (18.9)	10 (15.4)
Endocrine	1 (8.33)	2 (3.7)	3 (4.6)
Kidney and urinary	1 (8.33)	1 (1.9)	2 (3.1)
Cardiovascular	1 (8.33)	0	1(1.5)

Value show as N(%)

Table 2 Association between lithium toxicity and risk factor (logistic regression analysis)

Risk factor	Number of patients with lithium toxicity	Number of patients with no lithium toxicity	Odd ratio (95% CI)	p-value
Total dose/day	63	243	2.6 (1.5-4.5)	0.001
Butyrophenones	25	64	1.6 (0.9-2.9)	0.144
SSRIs	15	34	2.8 (1.3-6.1)	0.008
Schizophrenia	7	8	3.3 (1.1-10.1)	0.033
Anticonvulsants	3	7	1.0 (1.0-1.0)	0.631
Tricyclic antidepressants	1	10	0.5 (0.1-3.9)	0.480

Previous studies suggested that patients aged more than 60 years had a high risk of lithium toxicity because of altered pharmacokinetics, multiple medication especially ACE inhibitor and loop diuretics, renal impairment, and compliance such as medication confusion.[9-11,13] Conversely, the finding in this study showed that patients aged more than 60 years had no association risk with lithium toxicity. This might be affected by the small sample size that could not detect a significant difference for this factor. Similarly, lithium serum concentration exceeding 1.2 mEq/L also had no association with the risk for lithium toxicity in this study. Several reasons may explain this. Firstly, some patients might have signs and symptoms in the OPD cards so that toxicity could not be assessed. In addition, the physical examination may have revealed no abnormalities or subtle signs of toxicity for mild severity. The other reason is that the time at which blood samples are drawn is normally obtained 12 hours after the last dose and serum lithium levels are at steady state. Nevertheless, there were no records of blood collection time and whether lithium levels obtained were within the appropriate time frame. Thus some of excessive serum lithium levels may have been due to ingestion of lithium shortly before the blood sample was drawn. A previous study of the appropriateness of therapeutic drug monitoring (TDM) for lithium in psychiatric hospitals in Thailand indicated that education in encourage for hospital personnel on appropriateness of serum sample collection, interpretation, and proper use of serum drug levels was encouraged. Development of a request form containing pertinent data, such as time of the last dose, patient compliance and test results could help optimization of TDM use and reduction of unnecessary costs.[14]

Although the lithium serum concentration is used to evaluate the toxicity, a previous case report described severe lithium toxicity in a patient with normal serum concentration[15] or the delayed effect of cardiac complications while there was declining serum lithium concentration to normal level.[16] Conversely, the previous study of lithium levels and toxicity among hospitalized patients presented that only 27.8 percent of inpatients with excess lithium levels had signs and symptoms of toxicity[17] which was less than in this study (41.7% for inpatient). In general, close observation should be done in the cases of long term lithium therapy of patients who have risks regardless of lithium serum concentrations. Additionally, lithium toxicity can be avoided by conservative prescribing, intensive monitoring in combining drug therapy and educating patients to recognize early signs of lithium toxicity.

This study had some limitations. The retrospective study had incompleted information such as lithium plasma level and laboratory results. Some toxicities with require laboratory investigations such as renal function test which affects the lithium excretion, and thyroid function test and electrolyte imbalance, particularly hyponatremia, may predispose an individual to lithium toxicity. These parameters were not reported, especially for outpatient, because it is not a routine laboratory testing for outpatients or they were not identified as patients who are in risk.

In conclusion, the finding of this study supports that the use of lithium for treatment of bipolar disorder should be closely monitored especially in the patients who receive a dose of more than 900 mg/day, and the patients with schizophrenia and patients who received SSRIs drugs.

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