Iranian Journal of Pharmaceutical Sciences
2021: 17 (3): 71-82
www.ijps.ir

Original Article

Montmorillonite, a Promising New Material for Acute Lithium Intoxication in Rats

Mohammad Moshiri[a], Mohsen Imenshahidi[b,c] , Syed Adel Moallem[b,d], Ameneh Ghadiri[e], Abbas Nyasmand[f], Parisa Mirhoseini Moosavi[g], Mahmoud Gorji Valokola[b], Leila Etemad[c*]

[a]Medical Toxicology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran, [b]Department of Pharmacodynamics and Toxicology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran, [c]Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran, [d]Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Ahl Al Bayt, Karbala, Iraq, [e]Department of Internal Medicine and Medical Specialties,"Sapienza" University of Rome, Rome, Italy, [f]School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran, [g]Department of Soil Science, Faculty of Agriculture, Ferdowsi University of Mashhad, Mashhad, Iran.

Abstract

Lithium (Li) is considered the first-choice treatment for bipolar disorder and has a narrow therapeutic index therefore, a small increase in dose or plasma level can cause toxic effects. Gastrointestinal (GI) decontamination can be regarded as a first-line therapy for acute Li poisoning. Montmorillonite (MMT) is one of the best-known examples of a nanoclay that possesses unique properties for adsorbing substances, especially metals. We investigated the effects of MMT against acute Li intoxication. A single dose of Li (10 mEq/kg) was administered to the rats orally followed by oral gavage of MMT suspensions (0.5 or 1.0 g/kg) or activated charcoal (AC) (1g/kg) 5 min later. The serum Li concentration was measured at different times after treatment. Indeed, the serum level of sodium and potassium, WBC count, activity score, electrocardiogram, brain pathology changes, as well as pharmacokinetic parameters of Li, were evaluated. MMT at higher doses decreased the area under the curve (AUC), the elimination rate constant (Ka), the relative bioavailability (F), and increased the clearance of Li ($P<0.05$). MMT prevented Li induced leukocytosis, at the first sampling time, ($P<0.05$). It also exerted significant cardio protection, restored Li-induced ECG changes, heart rate alterations ($P<0.001$), and prevented Li induced hypoactivity. A similar amount of serum sodium and potassium concentration was observed in the animals. The results indicated that MMT reduced the absorption of Li, and slao possibly increased its clearance. Therefore, MMT may be a good candidate for decontamination, especially substances that are not well adsorbed by AC.

Keywords: Acute toxicity; Clay; Lithium; Montmorillonite, Chelation Therapy, Biological Availability.

Corresponding Authors: Leila Etemad, Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran,
Email: sfmojab@sbmu.ac.ir
Tel: +9821-88200061
Cite this article as: Moshiri M, Imenshahidi M, Moallem S. A., Ghadiri A, Nyasmand A, Mirhoseini Moosavi P, , Gorji Valokola M, Etemad L, *Montmorillonite, a Promising New Material for Acute Lithium Intoxication in Rats*, 2021, 17(3): 71-82.

1. Introduction

Since the late 1970s, lithium (Li), a monovalent cation, has been introduced for the treatment of a bipolar disorder. Li is also used in combination with other antidepressants drugs in order to treat major depressive

disorder [1]. Following oral administration in therapeutic dose, Li is rapidly absorbed, reaches maximum plasma concentrations in approximately 2 h, and excreted unchanged through the kidneys [2, 3]. Due to the narrow therapeutic index of Li, small changes in dose can cause side effects that in excessive consumption lead to induced neurological symptoms, including confusion, convulsions, seizures, and coma [4]. It also affects the cardiovascular system and changes electrocardiogram (ECG). Prolonged corrected QT interval (QTc), ST-segment elevation, and arrhythmia have been reported in patients with acute Li intoxication [5]. Indeed gastrointestinal (GI) side effects include nausea and diarrheas and hematological abnormalities, and typically leukocytosis, which are recognized as manifestations of Li toxicity [6].

There is no known antidote for Li poisoning. The treatment plan includes GI decontamination and supportive care. Gastric lavage can be effective in an acutely poisoned patient within one hour of ingestion. Activated charcoal (AC) does not effectively absorb Li and is not recommended unless toxic co-ingestants are suspected. Whole bowel irrigation is utilized if sustained release formulation has been ingested [7, 8].

The best-known example of a nano-clay is montmorillonite (MMT) that belongs to the smectite group of hydrous phyllosilicates [9]. There is an extensive isomorphous substitution for MMT that has 2:1-layer structure and high charge and cation exchange capacity (CEC). Cation-exchange reaction on MMT is rapid, thus cations can easily exchange with solute ions to change the cationic composition of the solution. The colloidal properties of the clays are due to the colloidal size and crystalline structure of layers. Clays have large specific surface area, excellent rheological characteristics and/or sorption properties [10]. Clay minerals with these unique characteristics can be used to absorb toxic substances that do not bind to AC thus it can prevent the accumulation of xenobiotics in organs [11-13]. Because of the adsorption capacity of MMT to heavy metals in addition to lack of effective options for GI decontamination, the efficacy of orally administrated MMT for acute Li detoxification was evaluated [12].

2. Material and Methods

Male Wistar rats weighing 250- 300 g (age, 10 weeks; n=36) were obtained from the Animal Center, School of Pharmacy, Mashhad University of Medical Sciences (MUMS). Animals were kept on a 12h/12h light/ dark cycle and room temperature. Animal experiments were approved by the Animal Care Committee of MUMS. Lithium carbonate (Li) (CAS Number: 554-13-2), ketamin (CAS Number: 1867-66-90), xylazin(CAS Number 7361-61-7)were obtained from sigma. AC was donated by the Department of Clinical Toxicology, Imam Reza Hospital, MUMS Mashhad, Iran.

2.1. Preparation and Characterization of MMT

As in our previous study, MMT was collected from a bentonite mine in the city of Ghaen, South Khorasan Razavee province, Iran. Briefly, thermal processing was used in order to remove all organic matter from samples. The purification methods were carried out through wet sedimentation, centrifugation and ultrasonication. MMT was purified from associated minerals like quartz, feldspar by the following process. Bentonite was suspended in distilled water to achieve clay particles, and then the clay suspension was stirred again and passed through the sieves at different sizes. Chemical treatment has been applied to reduce the impurities such as gypsum, salts and calcium carbonate and produce homogeneous interlayer cations. Particle size, X-ray, ratio peak of the quartz/MMT and CEC analysis showed that the purest fraction of MMT was separated from the raw bentonite [12].

2.2. Animal Study

The animals were divided into 5 groups of 6 rats. After a 12 hrs overnight fast, lithium carbonate was suspended in distilled water and then gavaged at the dose of 10 mEq/kg lithium [14]. Five minutes later, they were treated by distilled water (Li group), different does of MMT (0.5 or 1 g/kg) or AC (1g/kg) while the control group only received distilled water. All evaluations took place during two different time sequences, 2 and 24 hrs after treatment [12].

2.3. Hematological and Biochemical Parameters

The blood samples were taken through rat orbital sinus and cardiac puncture respectively. The total white blood cell (WBC) and serum elctrolites (Sodium and Potassium) were determined by using the auto analyzers of central laboratory of Imam Reza hospital of MUMS on blood samples that were taken at 2 and 24 hrs after treatment.

2.4. Pharmacokinetic Evaluations

The serum Li level (SLL) was evaluated after 15 minutes, 1, 2, 6, 12, 24 and 36 h after treatment. The SLL were determined using an auto analyzer in central laboratory of Imam Reza hospital of MUMS. The pharmacokinetic parameters of SLL were perfumed by PK solver 2 software. Then differences the means of parameters were statistically evaluated. The evaluated pharmacokinetic parameters were include: Area under the time-concentration curve (AUC), maximum concentration of SLL and its time (Cmax and Tmax) absorption rate constant (Ka), and clearance (CL). The Li relative bioavailability (F) of each group was calculated by dividing the mean AUCs of each group by the mean AUCs of Li group.

2.5. Electrocardiogram (ECG) and Heart Rate Recording

Briefly, the animals maintained under xylazine and ketamine anesthesia at 2 and 24 h after treatment and the ECG electrodes were attached to the dermal layer of both paws and legs. The ECG and heart rate were measured using a PowerLab Data Acquisition (AD

Instrument, Bella Vista, Australia) system under anesthesia. The ECG analyzed for changes in rate, rhythm, ST segment and T wave as well as measuring the PR and QTc intervals and QRS width. QTc was calculated by standard Bazett's formula [15].

2.6. Activity Score

According to our previous study, the animal's activity was scored at 2 and 24 h after treatment on a scale of 1 to 4. Grade 1: no voluntary movements even in response to painful stimuli, Grade 2: stretch movements in response to painful stimuli, Grade 3: stretch movements in response to stimuli, and Grade 4: spontaneous normal mobility [16].

2.7. Statistical Analysis

The results were reported as mean ± SEM. All data except activity scores analyzed using ANOVA, followed by the Tukey-Kramer test. The differences between the mean score of animal activity were evaluated by nonparametric statistical tests. The alpha level was set at 0.05. Data analysis was performed with SPSS Version 21.

3. Results and Discussion

3.1. Hematological and Biochemical Parameters

At the first evaluation time, Li administration increased the total number of WBC ($P<0.001$), while MMT at 0.5 g/kg and AC could not alleviate it. Administration of 1g/kg of MMT decreased the number of WBC in comparison with Li group ($P<0.05$). After 24 h, there were no significant differences in WBC counts between the control group and groups that received Li (Table 1).

At both sampling times, the level of sodium and potassium in different groups were similar to each other (Table 1).

Lithium treatment can be associated with a significant increase in WBC count in a dose-dependent manner [17, 18]. MMT at 1g/kg significantly decreased the Li absorption and Li induced leucocytosis.

The MMT has a minor adverse effect and there are enough evidence supporting the safety of short administration of MMT [19, 20]. Hypokalemia was reported as an important adverse effect induced by clay ingestion, due to potassium binding to mineral clay and reduction of potassium GI absorption. However, acute administration of MMT in our study did not change the serum potassium level as compared with other groups.

3.2. Electrocardiogram (ECG) and Heart Rate Recording

Two hours after Li gavage QTc prolongation and ST segment elevation were presented as compare to control group ($P<0.001$) (Table 2) (Figure 1). QTc interval increased in all Li treated groups except the group that received Li plus 1g/kg of MMT. MMT and AC treatment decreased the ST-segment elevation as compared with Li group ($P<0.001$) but only higher dose of MMT was capable of returning it to the control level. No significant differences in PR interval and QRS complex width were observed between Li treated groups and control group. In addition, T wave inversion did not also record after Li

exposure. Li administration induced a significant decrease in heart rate as compare to control group (P<001). MMT and AC treatment raised the heart rate in Li group (P<0.001). Higher dose of MMT restored heart rate significantly to near normal values (P<0001) However, the ECG changes reverted back to normal over a period of 24 h.

MMT markedly diminished Li induced ECG changes by reducing possible rate and extent of Li absorption. We observed the ECG changes comprising bradycardia, PR, QTc prolongation, and ST-segment elevation in Li intoxicated animals. According to the systematic review of 56 papers, the most common abnormal ECG in Li intoxicated patients was T wave inversion. Other ECG changes reported were sinus node dysfunction, sinoatrial blocks, PR and QT prolongation, ST elevation and ventricular tachycardia. The Li induced ECG abnormalities are related to SLL [21, 22] and acute Li toxicity can also cause bradycardia due to sinoatrial dysfunction [23-25]. In contrast to human reports, we did not observe T inversion in intoxicated animals.

3.3.Activity Score

At the first time of evaluation (2 h after treatment), Li administration reduced the activity (P<0.001). The activity of rats increased by MMT and AC treatment (P<0.001), however, MMT only at high dose could reach the activity to the normal level. At the second time (24 h after treatment) the levels of activity were normal in all groups (Figure 2).

3.4.Pharmacokinetic Evaluations

Administration of MMT at dose of 1g/kg significantly reduced the AUC of absorbed Li. MMT could increase the Tmax and reduce the Cmax of SLL. The rats that were treated by MMT had higher clearance (CL) rate than others (Table3).

Absorption and CEC of clay minerals seem to be promising candidates for the treatment of metal and xenobiotic toxicity. MMT is a type of cationic clays with a large internal area and high adsorption ability [26, 27]. *In vitro* absorption study showed that MMT binds with many heavy metals such as cadmium, chrome, cupper, manganese, nickel, lead, arsenic, and iron [12, 28-31]. Moreover, clay minerals can slow down the absorption of toxin from the GI tract because they are associated with high adsorption capacity along with poor or no absorption via the GI and adhering to the intestinal mucus [32].

The result of *in vitro* assay showed that Li is efficiently absorbed by MMT [33]. Adsorption of xenobiotics onto bentonite is limited to the surface of a clay particle therefore they can easily detach from them. Unlike bentonite, MMT can absorb the xenobiotic molecules into interlayer space rather than surface [34]. Li cation penetrates into the octahedral vacancies in the interlayer of MMT and was held by strong ionic bonds [35]. The higher dose of MMT was able to reduce all pharmacokinetic items of Li absorption as AUC, Cmax, Ka, and relative bioavailability in comparison with Li group. MMT also increased the Tmax and clearance rate of absorbed Li significantly. Binding Li to

MMT, especially in efficient dose of MMT, has prevented gastrointestinal absorption of Li resulted in slowing the rate of Li absorption and reduction of Ka. Inhibition of Li absorption by MMT delayed the time to reach maximum concentration and increased the Tmax and reduced the maximum SLL, and Cmax and eventually lower relative bioavailability (F). MMT improved the clinical manifestations of Li intoxicated rats.

It seems that, MMT could prevent the absorption of Li from the gastrointestinal track and also increased the clearance of Li. The Li clearance rate of MMT treated rats were significantly increased .The main rout of Li excretion and clearance is renal therefore increasing the clearance of Li by MMT administration may be due to removing Li from the circulation via gastric dialysis and need further researches [36, 37].

Osmotic properties of MMT produce a considerable increase in the volume of intestinal contents that increases the passage rate though GI tract [12, 32]. The most common adverse effect of AC is constipation. Although we did not use any scoring system to assess stool appearance consistency and frequency, the MMT treated groups did not show the consistency and frequency of stools compared to the control group. These findings are in line with our previous study [12].

4. Conclusion

MMT not only prevents the absorption of Li and reduces the AUC, Ka, and bioavailability of oral Li, but also increases the clearance of Li. According to the current and our previous animal studies and physicochemical properties of MMT (high CEC and few changes in bowel habits), it seems that MMT may be a good candidate for decontaminating of xenobiotics, especially substances that are not well adsorbed by AC. However, it is recommended to compare the absorption performance of MMT and AC with different materials.

References

[1] El-Mallakh RS and Jefferson JW. Prethymoleptic use of lithium. *Am. J. Psychiatry.* (1999):156: 29.

[2] Waring WS. Management of lithium toxicity. *Toxicol. Rev.* (2006) 25:221-30.

[3] Haussmann R, Bauer M, von Bonin S, Grof P and Lewitzka U. Treatment of lithium intoxication: facing the need for evidence. *Int. J. Bipolar. Disord.* (2015) 3:23.

[4] Adityanjee, Munshi KR and Thampy A. The syndrome of irreversible lithium-effectuated neurotoxicity. *Clin. Neuropharmacol.* (2005) 28:38-49.

[5] Prencipe M, Cicchella A, Del Giudice A, Di Giorgio A, Scarlatella A, Vergura M and Aucella F. [The acute renal and cerebral toxicity of lithium: a cerebro-renal syndrome? A case report]. *G. Ital. Nefrol.* (2013) 30.

[6] Oruch R, Elderbi MA, Khattab HA, Pryme IF and Lund A. Lithium: a review of pharmacology, clinical uses, and toxicity. *Eur. J. Pharmacol.* (2014) 740:464-73.

[7] Eshel G, Barr J, Chazan S, Tavori I, Kariv N, Schejter A, Greenberg R and Berkovitch M. Efficacy of orally administered deferoxamine, activated charcoal, and sodium bicarbonate in acute iron intoxication in rats: implications for the treatment of pediatric iron poisoning. *Curr. Ther. Res. Clin. Exp.* (2000) 61:648-56.

[8] Satar S, Topal M and Kozaci N. Ingestion of caustic substances by adults. Am. J. Ther. (2004)

11:258-61.

[9] Uddin F. Montmorillonite: An introduction to properties and utilization. In: Zoveidavianpoor M, editor. *Current Topics in the Utilization of Clay in Industrial and Medical Applications.* 3th London: Headquarters IntechOpen Limited; (2018) 1.

[10] Lopez-Galindo A, Viseras C and Cerezo P. Compositional, technical and safety specifications of clays to be used as pharmaceutical and cosmetic products. *Appl. Clay Sci.* (2007) 36:51-63.

[11] Dai W, Du HH, Fu LL, Liu HT and Xu ZR. Effect of montmorillonite on dietary lead (Pb) accumulation in tissues of tilapia (Oreochromis niloticus). *Appl. Clay. Sci.* (2010) 47:193-5.

[12] Moosavi PM, Astaraei AR, Karimi A, Moshiri M, Etemad L, Zeinali M and Karimi GR. Efficacy of orally administered montmorillonite for acute iron poisoning detoxification in rat. *Appl. Clay Sci.* (2015) 103:62-6.

[13] Han Z, Li J, Zhang M and Chunxia LV. Effect of montmorillonite on arsenic accumulation in common carp. *Afr. J. Biotechnol.* (2012) 11:6160-8.

[14] Morrison JM, Jr., Pritchard HD, Braude MC and D'Aguanno W. Plasma and brain lithium levels after lithium carbonate and lithium chloride administration by different routes in rats. *Proc Soc Exp Biol Med*. (1971) 137:889-92.

[15] Kmecova J and Klimas J. Heart rate correction of the QT duration in rats. *Eur. J. Pharmacol.* (2010) 641:187-92.

[16] Moshiri M, Vahabzadeh M, Etemad L and Hosseinzadeh H. Failure of Intravenous Lipid Emulsion to Reduce Diazinon-induced Acute Toxicity: a Pilot Study in Rats. *Iran J. Pharm. Res.* (2013) 12:897-902.

[17] Amitai M, Zivony A, Kronenberg S, Nagar L, Saar S, Sever J, Apter A, Shoval G, Golubchik P, Hermesh H, Weizman A and Zalsman G. Short-term effects of lithium on white blood cell counts and on levels of serum thyroid-stimulating hormone and creatinine in adolescent inpatients: a retrospective naturalistic study. *J. Child Adolesc. Psychopharmacol.* (2014) 24:494-500.

[18] Carmen J, Okafor K and Ike E. The effects of lithium therapy on leukocytes: a 1-year follow-up study. *J. Natl. Med. Assoc.* (1993) 85:301-3.

[19] Wang JS, Luo H, Billam M, Wang Z, Guan H, Tang L, Goldston T, Afriyie-Gyawu E, Lovett C, Griswold J, Brattin B, Taylor RJ, Huebner HJ and Phillips TD. Short-term safety evaluation of processed calcium montmorillonite clay (NovaSil) in humans. *Food Addit. Contam.* (2005) 22:270-9.

[20] Gao X, Miao R, Tao Y, Chen X, Wan C and Jia R. Effect of Montmorillonite powder on intestinal mucosal barrier in children with abdominal Henoch-Schonlein purpura: A randomized controlled study. *Medicine (Baltimore)*. (2018) 97:e12577.

[21] van Noord C, Straus SM, Sturkenboom MC, Hofman A, Aarnoudse AJ, Bagnardi V, Kors JA, Newton-Cheh C, Witteman JC and Stricker BH. Psychotropic drugs associated with corrected QT interval prolongation. *J. Clin. Psychopharmacol.* (2009) 29:9-15.

[22] Mehta N and Vannozzi R. Lithium-induced electrocardiographic changes: A complete review. *Clin. Cardiol.* (2017) 40:1363-7.

[23] Tilkian AG, Schroeder JS, Kao JJ and Hultgren HN. The cardiovascular effects of lithium in man. A review of the literature. *Am. J. Med.* (1976) 61:665-70.

[24] Armstrong EJ, Dubey A, Scheinman MM and Badhwar N. Lithium-associated Mobitz II block: case series and review of the literature. *Pacing Clin. Electrophysiol.* (2011) 34:e47-51.

[25] Goldberger ZD. Sinoatrial block in lithium toxicity. *Am. J. Psychiatry.* (2007) 164:831-2.

[26] Babich H and Stotzky G. Reductions in the toxicity of cadmium to microorganisms by clay minerals. *Appl. Environ. Microbiol.* (1977) 33:696-705.

[27] Abollino O, Aceto M, Malandrino M, Sarzanini C and Mentasti E. Adsorption of heavy

metals on Na-montmorillonite. Effect of pH and organic substances. *Water Res.* (2003) 37:1619-27.

[28] Subramanian B and Gupta G. Adsorption of trace elements from poultry litter by montmorillonite clay. *J. Hazard. Mater.* (2006) 128:80-3.

[29] Bhattacharyya KG and Gupta SS. Influence of acid activation on adsorption of Ni (II) and Cu (II) on kaolinite and montmorillonite: kinetic and thermodynamic study. *Chem. Eng. J.* (2008) 136:1-13.

[30] Chen Y, Wang S, Li Y, Liu Y, Chen Y, Wu Y, Zhang J, Li H, Peng Z, Xu R and Zeng Z. Adsorption of Pb(II) by tourmaline-montmorillonite composite in aqueous phase. *J. Colloid. Interface. Sci.* (2020) 575:367-76.

[31] Javdani H, Khosravi R, Etemad L, Moshiri M, Zarban A and Hanafi-Bojd MY. Tannic acid-templated mesoporous silica nanoparticles as an effective treatment in acute ferrous sulfate poisoning. *Microporous and Mesoporous Materials*. (2020) 307:110486.

[32] Carretero MI. Clay minerals and their beneficial effects upon human health. A review. *Appl. Clay. Sci.* (2002) 21:155-63.

[33] Bujdák J, Slosiariková H, Nováková L and Číčel B. Fixation of lithium cations in montmorillonite. *Chem. Zvesti.* (1991) 45:499-507.

[34] Weber JB. Molecular structure and pH effects on adsorption of 13 s-triazine compounds on montmorillonite clay. *Am. Mineral.* (1966) 51:1657-70.

[35] Wungu TD, Aspera SM, David MY, Dipojono HK, Nakanishi H and Kasai H. Absorption of lithium in montmorilnite: a density functional theory (DFT) study. *J. Nnsci. Nanotechnol.* (2011) 11:2793-801.

[36] Harward HA. chapter 70, Lithium. In: Nelson LS, Howland MA, lewin NA, Smith SW, Goldfrank LR and Homan RS, editors. *Goldfranks' Toxiclogy Emergencies1th Ed* New York: Mc Grow Hill; (2019). p. 1065-75.

[37] Coopr JM, Duffull SB, Saiao AS and Isbister GK. The phrmacokinetics of sertraline in overdose and the effect of activated charcoal. *Br. J. Clin.*

Tables:

Table 1. Total of white blood cell (WBC), serum sodium (Na+) and potassium (K+) levels in lithium (Li) (10 mEq/kg) intoxicated rats that were gavaged with distilled water, montmorillonite(MMT) (0.5 or 1 g/kg) or activated charcoal (AC) (1g/kg). Rats of control group were treated by distilled water.

Group treatment	Total WBC ($x10^3$/ML)		Na+ (mEq/L)		K+(mEq/L)	
	2 hours	24 hours	2 hours	24 hours	2 hours	24 hours
Control	8.5±1.1	8.7±0.8	137.5±6.4	137.8±6.9	4.23±0.84	5.7±0.62
Li +distilled water	14.1±0.9**	11.2±1.3	139.2±5.8	137.0±6.3	5.4±0.64	4.98±0.61
Li+ MMT (0.5g/kg)	13.6±1.2*	8.9±1.1	136.7±7	140.5±5.6	4.86±1	5.5±0.9
Li + MMT (1g/kg)	9.5±1#	9.3±1	141.2±6.4	136.9±6.2	5.6±0.86	4.65±1.01
Li +AC (1g/kg)	13.7±0.9*	9.4±1.3	134±5.4	142.2±5.2	4.1±0.7	5.7±0.9

All values are presented as mean ±SEM. *P<0.05, **P<0.01 compared to the control group, #P<0.05 compared to the Li group. Tukey–Kramer test, n=6.

Table 2. Electrocardiogram and heart rate values measured in in lithium (Li) (10 mEq/kg) intoxicated rats that were gavaged with distilled water, montmorillonite (MMT) (0.5 or 1 g/kg) or activated charcoal (AC) (1g/kg) at 2 h after treatment. Rats of control group were treated by distilled water.

Groups	**PR interval (m sec)**	**QTc(msec)**	**QRS complex width (msec)**	**ST elevation (m v)**	**Heart rate (beats/min)**
Control	50 ± 0.9	120±5.2	200±6.2	0.03±0.0034	350±6.1
Li	53 ± 0.8	220±4***	210±5.3	0.15±0.0058***	200±5.9***###
Li + MMT (0.5g/kg)	52 ± 1	196.38±5.1***#	215±5.9	0.1±0.0031***###	250±4.6***###
Li + MMT (1g/kg)	50 ± 0.95	117.67±4.8###	213±6	0.03±0.0026###	330±6.5###

Li + AC	52 ± 0.85	180±5.9***###	217±6.3	0.1±0.0037***###	257±5.2***###

Each value represents the mean+ SEM. ***P<0.001 compared with control group and # p<0.05, ### p<0.001 Compared with Li group. Tukey–Kramer test, n=6.

Table 3. Pharmacokineticparametersof lithium (Li) in oral Li (10 mEq/kg) intoxicated rats that were gavaged with distilled water, montmorillonite(MMT) (0.5 or 1 g/kg) or activated charcoal (AC) (1g/kg) five minute after Li.

	Lithium	AC	MMT 0.5g/kg	MMT1g/kg
AUC (mmol/L*h)	156.39± 10.5	130.6 ±9.6	119.53 ±10.2 *	108.82 ±7.25 **
Cmax (mmol/l)	4.72 ±0.24	4.22 ±0.33	3.87 ±0.40	3.69 ±0.29 *
Tmax(hours)	9.62 ±0.71	8.15 ± 0.75	9.57 ±1.0	12.51±0.8 *
F (%)	100	83.5	76.43	69.58
CL((mEq/kg)/(mmol/L)/h)	3.0 E-6 ± 1.0 E-8	0.0053± 2E-6	0.0269±0.001*	0.0420±0.0029*
Ka(1/h)	0.882 ±0.7	0.772 ± 0.12	0.373 ± 0.09 *	0.197 ± 0.06 **

AUC =Area under the time-concentration curve, CL=clearance, Cmax = Maximume serum Li level, F= relative bioavailability, Ka = absorption rate constant, and Tmax= time of maximum serum Li level. *P<0.05, **P<0.01 compared to the Li group.

Figures:

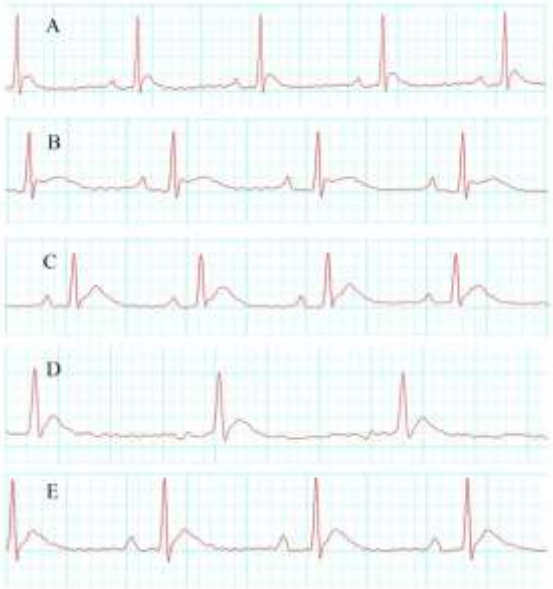

Figure1. Effect of Montmorillonite (MMT) or activated charcoal (AC) on Lithium (Li) induced electrocardiogram (ECG)changes in ratat 2 h after intoxication. The ECG showed ST segment elevation and QTc prolongation after Li administration. Restoration of ST segment elevationand QTc prolongationwere observed with MMT especially at high dose. The animal received distilled water (A, control), Li at 10 mEq/kg(B), Li + MMT at 0.5g/kg (C), Li+MMT at 1g/kg (D) or Li +AC (1g/kg).

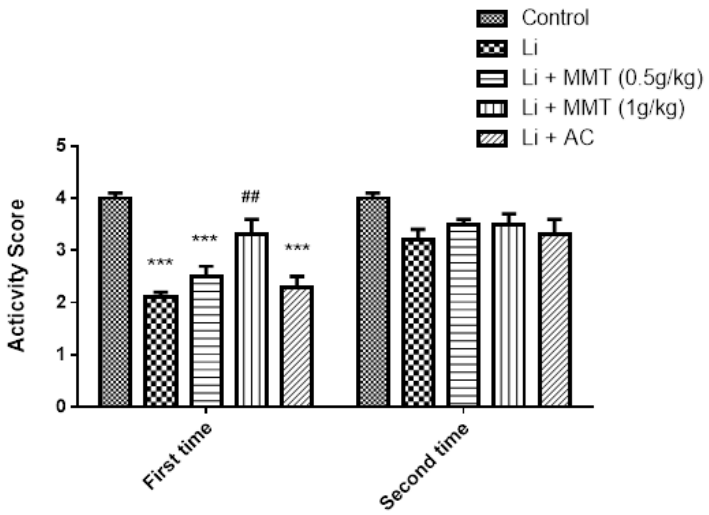

Figure 2. Activity score of lithium (Li) (1g/kg) intoxicated rats that were gavaged with distilled water (Li group), montmorillonite (MMT) (0.5 or 1 g/kg) or activated charcoal (AC) (1g/kg) at 2 and 24 h (First and second time) after treatment. Rats of control group were treated by distilled water. The results are reported as mean ± SEM, *P<0.05, ***P<0.001 compared to the control group, #P<0.05 compared to the Li group. Kruskal –Wallis test, n=6

ONLINE SUBMISSION

www.ijps.ir