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Treatment of acute lithium intoxication with high-flux hemodialysis membranes

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SUMMARY

Lithium carbonate is commonly prescribed for the treatment of bipolar (manic-depressive) disorders. However, because of its narrow therapeutic index an excessive elevation of serum lithium concentration, either during chronic maintenance therapy or after an acute overdose, can result in serious toxicity. In addition to supportive care, the established treatment of severe lithium toxicity is haemodialysis. Conventional haemodialysis can reduce serum lithium rapidly, but post-dialysis rebound elevations with recurrent toxicity have been documented in old publications. High-flux membranes should be capable of removing more lithium per hour of haemodialysis, but published values are not available. We report here three patients with acute lithium intoxication who were treated successfully with bicarbonate and high-flux haemodialysis membranes. Our patients presented with a severe degree of intoxication, based on the amount of drug ingested, the initial serum lithium level, the severity of neurologic symptoms and systemic manifestations. Two patients developed acute renal failure probably as a result of volume depletion since it was rapidly reversible by haemodialysis and infusion therapy. In addition, consecutive haemodialysis sessions and improvement of renal function allowed a rapid decrease in serum lithium levels without haemodynamic instability or rebound elevations in lithium concentration. The effectiveness of the procedure in these cases can be attributed to the use of bicarbonate dialysate and high-efficiency dialysers. This is the first report describing the effect of high-efficiency dialysers on lithium pharmacokinetic. Using this technique the elimination rate of lithium was found to be greater than previously reported with haemodialysis.

Key words: ***Acute renal failure. Bicarbonate. Haemodialysis. High-flux membranes. Lithium intoxication. Pharmacokinetics.***

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TRATAMIENTO DE LA INTOXICACION AGUDA POR LITIO MEDIANTE HEMODIALISIS CON DIALIZADORES DE ALTA EFICIENCIA

RESUMEN

El carbonato de litio se utiliza de forma habitual para el tratamiento de los trastornos bipolares (maniaco-depresivos). Sin embargo, debido a su estrecho margen terapéutico la elevación de los niveles séricos, bien durante la terapia crónica de mantenimiento o después de una sobredosis aguda, puede dar lugar a toxicidad grave. En la intoxicación aguda severa por litio el tratamiento establecido es la hemodiálisis, que permite la eliminación rápida de la droga. Las membranas de alto flujo deben ser capaces de eliminar más litio por hora de hemodiálisis, pero existen pocas evidencias al respecto. Se presentan tres pacientes con una intoxicación aguda por litio con riesgo vital, complicada en dos de ellos por insuficiencia renal, que fueron tratados con éxito mediante hemodiálisis intermitente diaria con membranas de alto flujo. Las técnicas actuales de hemodiálisis, utilizando dializadores de alta eficiencia y baño de diálisis con bicarbonato, permiten una eliminación excelente del litio sin el rebote que típicamente se observaba en el pasado tras la hemodiálisis convencional. La hemodiálisis debe ser instaurada precozmente en cualquier paciente con intoxicación por litio que presente coma, convulsiones, fallo respiratorio, deterioro del estado mental, y especialmente si la función renal está comprometida.

Palabras clave: ***Bicarbonato. Farmacocinética. Fracaso renal agudo. Hemodiálisis. Intoxicación por litio. Membranas de alto flujo.***

INTRODUCTION

Lithium carbonate is useful for treatment of bipolar disorders (maniac-depressive), but due to its narrow therapeutic window, raise in lithium serum levels, either during chronic maintenance therapy or during an acute overdose, may lead to severe toxicity. Besides general support measures, established therapy for severe lithium toxicity is hemodialysis. Conventional hemodialysis rapidly reduces lithium serum levels[1-6], although sometimes a post-dialysis rebound is observed, with an increase in lithium serum levels and toxicity recurrence. High-flux membranes should be able to clear up more lithium per dialysis hour, although there are no evidences so far showing this.[5,7,8] We present three patients with acute lithium toxicity successfully treated with high-flux hemodialysis membranes. The effect of these dialyzers in lithium pharmacokinetics allowed for a rapid decrease in serum levels, with no significant rebound. These cases illustrate that current hemodialysis therapies are effective for acute lithium toxicity in which the use of extracorporeal techniques is indicated.

CLINICAL CASES

Case 1

Twenty-nine years old woman with a history of bipolar disorder treated with lithium salts, admitted for suicidal attempt. Her current treatment was mirtazapine 30 mg/day, reboxetine 8 mg/day, and clonazepam 4 mg/day. About 20 hours after the intake of 100 tablets of lithium carbonate 400 mg, she was found unconscious at home. At admission she had stupor, tremor, and confusion. Blood pressure was 100/60 mmHg, heart rate 120 bpm, and urine output of 15mL/h. After several cycles of gastric lavage with activated charcoal, lithium levels were 5.83 mmol/L. Other laboratory findings were: hematocrit 51%, hemoglobin 17.6 g/dL, platelets 3000,000/mm^3, urea 106 mg/dL, creatinine 5.7 mg/dL, Na 132 mmol/L, K 7 mmol/L, bicarbonate 20 mmol/L. One thousand mL of isotonic saline, 250 mL of 1/6 molar bicarbonate, and 1000 mL of 10% dextrose solution with 45 IU of insulin was infused. At the Intensive Care Unit (ICU) she was monitored and 4 hours after admission she was hemodialysed with a 1.5-m^2 cellulose triacetate membrane dialy-

zer, bicarbonate bath, blood flow of 150 mL/min, and dialyzate flow of 500 mL/min. During the three hours of hemodialysis, 1200 mL were ultrafiltrated and replaced with isotonic saline, remaining hemodynamically stable and with urine output of 80-110 mL/h. Post-dialysis lithium level was 5.22 mmol/L, and 20 hours later 4.46 mmol/L, receiving a second hemodialysis with a 1.36 m^2 high permeability polysulfone membrane and blood flow of 180 mL/min. During the 4 hours of hemodialysis, 2000 mL were ultrafiltrated that were replaced with isotonic saline. Post-dialysis lithium level was 2.48 mmol/min. During the following hemodialysis sessions, lithium levels decreased from 1.82 to 0.84, and from 1.02 to 0.5 mmol/min, after 6 and 4 hours of hemodialysis, respectively. Hemodialysis therapy ended when lithium level was 0.5 mmol/min, needing four sessions in total.

Forty-eight hours after admission, the patient developed profound stupor requiring mechanical ventilation, with consciousness recovering within the next five days, and being extubated within 11 days, and within 14 days tremor had disappeared, although she remained with bradypsychia. At discharge, neurological status was recovered, with no sequelae, and brain magnetic resonance imaging being normal.

Case 2

Thirty-five years old woman diagnosed with bipolar disorder, treated with lithium carbonate and risperidone, admitted for suicidal attempt. She was brought to the emergency room 24 hours after the intake of 40 g of lithium carbonate. Before admission, she had begun with vomiting, diarrhea, drowsiness, and stiffness. She was conscious, mildly disoriented, with generalized hypertonia and hyperreflexia, with clonus and bilateral positive Babinsky's sign. Serum lithium level was 7.96 mmol/L, and creatinine was 3.2 mg/dL. Four hemodialysis sessions were required with 2-m^2 PMMA membranes, until de fifth admission day in which lithium levels were < 1 mmol/L. Within the fourth day, renal function was normal. At 48 hours after admission, lower limb osteotendinous reflexes were abolished, with generalized tremor, sweating, tachychardia, tachypnea, hemodynamic instability, ocular motor disorders, and decreased consciousness level. She was transferred to the ICU and connected to mechanical ventilation, being in an arreactiva coma status, the EEG showing finding of generalized brain impairment. Body temperature rose to 39.5º C still in spite of anti-thermals and physical measures. Brain CT and lumbar puncture were normal. Before the evidence of a malignant neuroleptic syndrome, dantrolene therapy (60 mg/6 h iv) was started, and the hypertonia subsided but with persistent hyperthermia for seven days. She had evidence of rhabdomyolysis and CPK levels reached 23,000 U/L. During the 43 days of hospitalization she also had hospital-acquired infections and multiorgan dysfunction requiring vasoactive drugs and high FiO_2 levels. After being for 18 days in an arreactiva coma state, progressive neurologic recovering began. At discharge from the ICU, infectious, hemodynamic, and ventilatory complications had resolved and she only had mild dysarthria and dysmetria.

Case 3

Forty-three years old man with bipolar disorder treated with lithium carbonate, admitted to the hospital for suicidal attempt after the intake of 50 tablets of lithium carbonate 400 mg, 45 tablets of clonazepam 2 mg, and 10 tablets of clorazepate 10 mg. At admission, 4 hours after the intake, he was drowsy and confused, with a 15-point score in Glasgow's scale. Blood pressure was 105/600 mmHg, heart rate was 90 bpm, and he had adequate urine output. After gastric lavage with activated charcoal, lithium serum level was 3.62 mmol/L. Other laboratory findings were: hematocrit 47%, hemoglobin 16 g/dL, platelets 200,000/mm^3, urea 17 mg/dL, creatinine 0.8 mg/dL, Na 140 mmol/L, K 4 mmol/L, bicarbonate 27 mmol/L. Three thousand milliliters of isotonic saline were infused and 3 hours after admission hemodialysis was started with a low-ultrafiltration polyamide membrane dialyzer (Polyflux 21 L), dialysis fluid with bicarbonate, blood flow of 280 mL/min, and dialyzate flow of 500 mL/min. During the 5 hours of hemodialysis, 3000 mL were ultrafiltrated that were replaced with isotonic saline. During and after the hemodialysis session, the patient remained hemodynamically stable and with polyuria. Post-dialysis lithium went down to 3.37 mmol/L, receiving a second 6-h hemodialysis with high ultrafiltration polyamide membrane dialyzer (polyflux 210H) and blood flow of 280 mL/min. Three thousand and five hundred milliliters were ultrafiltrated that were replaced with isotonic saline, maintaining a urine output of 150 mL/h. The post-dialysis lithium level was 1.19 mmol/L. Within the following days, with forced alkaline diuresis, lithium levels were kept below 1 mmol/L and the neurological state was completely recovered.

METHODS

Lithium serum levels were analyzed from samples obtained pre- and post-hemodialysis, and each after the end of dialytic therapy. Determinations were done by means of atomic absorption spectrometry. Serum lithium therapeutic range was 0.4-1.2 mmol/l. In order to determine specific pharmacokinetic parameters for each patient, serum lithium levels pre- and post-hemodialysis were used, and constant lithium clearance rate (K_{cl}) and lithium half-life ($T_{1/2}$) were calculated during and after hemodialysis sessions by means of standard equations:

$$K_{cl}\ (h^{-1}) = 1/\text{time} * \ln (L1/L2);\ T_{\_} = 0{,}693/K_{cl},$$

Where «time» is the number of hours between lithium levels «L1» and «L2».[1,3]

RESULTS

Pre- and post-dialysis lithium levels for the three cases, are shown in Figures 1, 2, and 3, respectively. In the three cases, an important decrease in lithium serum levels was observed with intermittent hemodialysis, and in no case there was a significant rebound throughout the clinical course. Lithium K_{cl} and $T_{1/2}$ during and after hemodialysis sessions are shown in Tables I, II, and III. The tables show how during the clearance phase lithium half-life with hemodialysis varied between 2.64-5.72 hours, representing a value that was 5-40 times lower as compared to exclusive renal clearance.

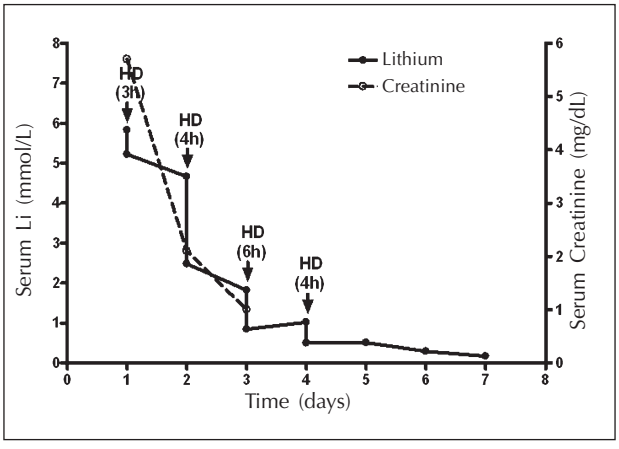

Fig. 1.—Lithium and creatinine levels in Case 1. The arrow indicates the time of each hemodialysis (HD) and the number of hours is shown between brackets.

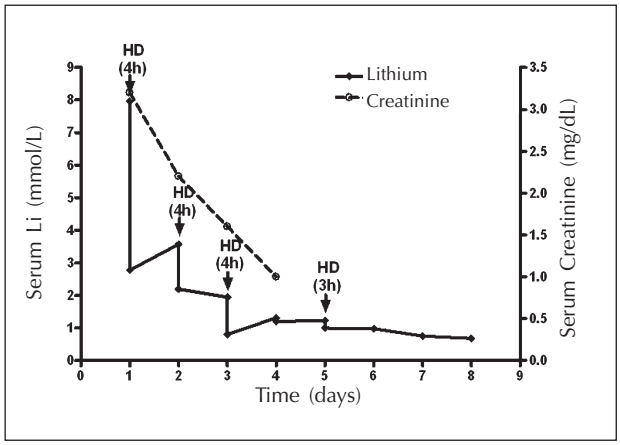

Fig. 2.—Lithium and creatinine levels in Case 2. The arrow indicates the time of each hemodialysis (HD) and the number of hours is shown between brackets.

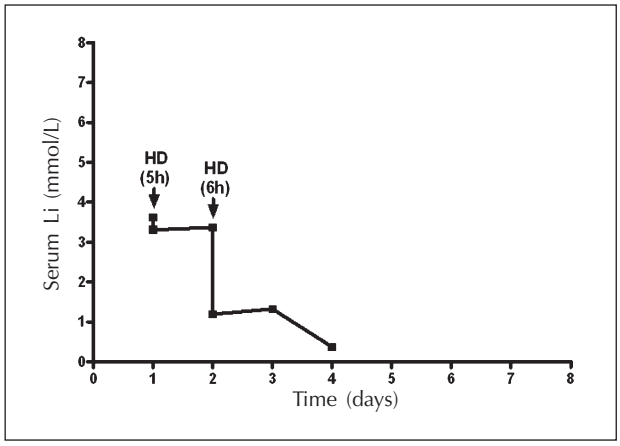

Fig. 3.—Lithium levels in Case 3. The arrow indicates the time of each hemodialysis (HD) and the number of hours is shown between brackets.

Table I. Lithium pharmacokinetics during and after hemodialysis (HD) in case 1

Period	K (h^{-1})	$T_{1/2}$ (hours)
During 1st HD (CT)	0.036/h	18.81
After 1st HD (renal excretion)	0.056/h	122.13
During 2d HD (PS)	0.157/h	4.39
After 2d HD (renal excretion)	0.015/h	44.79
During 3d HD (PS)	0.028/h	5.37
During 4th HD (PS)	0.078/h	3.88
After 4th HD (renal excretion)	0.023/h	29.46

CT = cellulose triacetate; PS = polysulfone
K(h^{-1}) = clearance rate, $T_{1/2}$ = half-life.

Table II. Lithium pharmacokinetics during and after hemodialysis (HD) in case 2

Period	K (h^{-1})	$T_{1/2}$ (hours)
During 1st HD (PMMA)	0.262/h	2.64
During 2d HD (PMMA)	0.121/h	5.72
After 2d HD (renal excretion)	0.0082/h	83.87
During 3d HD (PMMA)	0.219/h	3.15
After 3d HD (renal excretion)	0.0097/h	71.11
During 4th HD (PMMA)	0.069/h	10.04
After 4th HD (renal excretion)	0.012/h	57.24

PMMA = poly methyl methacrylate
K(h^{-1}) = clearance rate, $T_{1/2}$ = half-life.

Table III. Lithium pharmacokinetics during and after hemodialysis (HD) in case 3

Period	K (h^{-1})	$T_{1/2}$ (hours)
During 1st HD (Polyflux 21 L)	0.022/h	30.96
During 2d HD (Polyflux 21 H)	0.138/h	4.99
After 2d HD (renal excretion)	0.035/h	19.61

K(h^{-1}) = clearance rate, $T_{1/2}$ = half-life.

DISCUSSION

Lithium carbonate is a 74 Da salt that after oral administration is almost completely absorbed within the next 8 hours, its clearance being essentially through the kidney by glomerular filtration. Lithium is a small ion (7 Da) that does not bound to proteins, and its distribution volume is approximately 0.8 L7kg, very similar to that of body water, which allows for the effectiveness of hemodialysis as a clearance mechanism. After a single dose, lithium clearance half-life is 12-27 hours, but it may be prolonged to 58 hours in elderly patients and in those receiving lithium chronically.[3] In normal subjects, lithium renal clearance is 10-40 mL/min.[3,5] Toxicity occurrence is related with high lithium serum concentrations: mild toxicity appears with lithium levels above 2.5 mmol/L. severe toxicity occurs with levels between 2.5-3.5 mmol/L, and life-threatening toxicity may occur with levels above 3.5 mmol/L. The lethal dose in unknown, although one of the cases with the highest lithium levels (10.6 mmol/L) was only treated with forced diuresis and he survived.[9] In order to accelerate lithium clearance, when levels are higher than 3.5 mmol/L in acute intoxication, some modality of extra-renal depuration is required.

Due to its pharmacokinetics, the clinical effects of lithium toxicity vary according to the type of intoxication. Lithium uptake by the different tissues varies and diffusion between intra- and extracellular compartments is slow.[10] Whereas in acute intoxication symptoms tend to resolve rapidly, in chronic intoxication and in acute intoxication over a chronic therapy, where a greater proportion of lithium is in the intracellular compartment, the symptoms are more severe and toxicity tends to resolve more slowly, as lithium is redistributed out of the intracellular compartment.[1] Lithium diffusion is rapid from liver to the kidneys, but more slowly from brain, muscle, or bone, reaching the steady state between tissues and serum within several days.[1,10] Lithium half-life also shows high variability that depends on the type of intoxication.

Established treatment for severe acute lithium intoxication is hemodialysis.[1-6,11,12] Lithium clearance by hemodialysis is much higher than the one produced endogenously by the kidney, even with forced diuresis. In normal individuals, renal lithium clearance is 10-40 mL/min. Lithium clearance by intermittent hemodialysis varies between 70-170 mL/min.[3] Although hemodialysis markedly decreases lithium half-life, occasionally there was a rebound in serum levels several hours after the dialysis session when lithium diffused out of the cells. This is a reflection of a slower steady state through cellular membranes than through the dialyzer membrane. The rebound may also be due to a delay in gastrointestinal absorption of the intake of slow-releasing lithium. In the past, hemodialysis with acetate bath might have contributed to lithium rebound. Acetate would reduce lithium cellular flux promoting its intracellular accumulation. By diffusing into the cells as acetic acid, acetate induces intracellular acidosis and activation of the sodium-proton carrier.[5,13] Protons are carried out of the cell whereas lithium is carried into the cell replacing sodium. Once acetate has been metabolized, intracellular lithium would increase extracellular lithium levels.[2]

Our patients presented a severe degree of intoxication, in view of the amount of drug consumed, initial lithium serum levels, the presence of renal failure in two of them, and the severity of neurologic symptoms and other systemic manifestations. Cases 1 and 2 presented with acute renal failure, likely due to volume depletion that was corrected with volume infusion and early hemodialysis. The worsening of neurologic symptoms in both cases, hours after having started dialysis therapy, may have been delayed because of slow lithium distribution into the brain.[14] However, consecutive hemodialysis sessions and renal function improvement allowed for a rapid decrease in lithium serum levels, with no hemodynamic instability or significant rebounds in serum le-

vels. Case 3, with a less severe intoxication, only required tow hemodialysis sessions. The great difference between lithium serum levels achieved after the first and second hemodialysis sessions in this patient could be partially explained by the fact that during the first session lithium was still in its absorption-distribution phase. Another explanation could be that the membrane used in the first session was of low ultrafiltration and of high ultrafiltration in the second one. High ultrafiltration membranes allow for greater clearance of small molecules such as urea, creatinine, and lithium, by adding to the connective component. In these three cases, treatment efficacy could be attributed to the use of high efficiency dialyzers that rapidly clear plasmatic lithium establishing then a maximum gradient between the intracellular and the extracellular spaces, and to the bicarbonate bath, which prevents accumulation of intracellular lithium and promoted its extrusion.

In acute intoxications, the effect of conventional hemodialysis on lithium pharmacokinetics[1,4] showed a half-life of 3.6-5.7 hours, whereas during renal excretion half-life varied between 28-197 hours. In our cases, the decrease in lithium serum levels (and therefore of its half-life) during the first hemodialysis session was highly variable, reflecting that one patient still was in the lithium absorption-distribution phase. When all three patients were in the elimination phase, hemodialysis with high flow membranes reduced lithium half-life 10-40 fold as compared to only renal excretion.

By achieving a slow clearance, continuous therapies would contribute to a more complete depuration of intracellular lithium preventing post-dialysis rebound and offering an advantage over intermittent hemodialys.[15-22] However, after discontinuation of continuous arteriovenous hemodiafiltration, a rebound has also been observed with increase in lithium levels.[16] In the case of acute intoxication with very high lithium serum levels, continuous therapies do not reduce lithium levels as rapidly as hemodialysis and they are often limited by the need of prolonged anticoagulation that may contribute to severe complications. With continuous hemodiafiltration lithium clearances of 38-62 mL/min have been reported,[17,18] which are not much higher than just renal clearance. On the other hand, the lactate-based alkalinizing agent[20,23,24] used in some continuous therapies may also decrease lithium cellular flow (similar to acetate) by inducing intracellular acidosis and stimulating lithium-proton transport.[15-17,20] Continuous therapies may be useful in patients with chronic toxicity (or acute intoxication over chronic toxicity) with no life-threatening risk, and in which intracellular lithium accumulation may represent an important risk of permanent sequelae.

In severe acute lithium intoxication hemodialysis is preferred over continuous therapies. Hemodialysis offers the advantage of a more rapid lithium depuration, it may also clear more rapidly other concomitantly consumed drugs, it may clear other uremic toxins, and it may rapidly correct associated acid-base and water and electrolytes unbalances. In this context, force alkaline diuresis and the use of bicarbonate bath prevent intracellular acidification and the resulting activation of sodium-proton (or lithium-proton) carriers, and thus the lithium intracellular accumulation.[2,5] Early hemodialysis with bicarbonate bath and high flow membranes (polysulfone, polyamide, PMMA, etc.), which have greater clearance capability of small molecules by combining diffusion and convection, has shown to be the first choice therapy for severe acute lithium intoxication. An alternative could be the combination of hemodialysis followed by continuous hemodiafiltration.[21] In this way, hemodialysis provides a rapid initial lithium clearance in order to achieve early resolution of symptoms. The use of continuous hemodiafiltration after hemodialysis would allow for lithium clearance as it reaches the extracellular compartment. Another cheaper alternative would be the so-called slow prolonged hemodialysis for 6-8 hours daily.

In summary, modern hemodialysis techniques, using high efficiency dialyzers and bicarbonate dialysis bath, allow for an outstanding lithium clearance without the rebound typically observed in the past after conventional hemodialysis. Hemodialysis should be initiated early in any patient with lithium intoxication presenting with coma, seizures, respiratory failure, mental state impairment, and especially when renal function is compromised.

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