

Comparison of patients hemodialyzed for lithium poisoning and those for whom dialysis was recommended by PCC but not done: What lesson can we learn?

B. Bailey¹ and M. McGuigan²

¹*Divisions of Clinical Pharmacology and Toxicology and of Emergency Medicine, Department of Pediatrics, Hôpital Ste-Justine, Montréal, Québec, and*

²*Division of Clinical Pharmacology and Toxicology, Department of Pediatrics, The Hospital for Sick Children and The Ontario Regional Poison Information Centre, Toronto, Ontario, Canada*

Key words

lithium – poisonings –
poison control centre –
hemodialysis – outcome

Abstract. **Aims:** To compare patients for whom hemodialysis was done for lithium poisoning and those for whom it was recommended by the poison control centre (PCC) but not done and to evaluate the effect of withholding hemodialysis on outcomes. **Methods:** All lithium overdoses brought to the attention of the PCC were prospectively followed from January 1 to December 31, 1996. Patients for whom hemodialysis was done were compared with those for whom it was recommended but not done in terms of clinical presentation, lithium elimination half-life, need for transfer to another centre for hemodialysis, and outcome (death, or sequel or recovery). **Results:** A total of 205 cases of lithium overdoses were collected including 110 with levels higher than 1.5 mmol/l. There were 12 acute lithium overdoses; no patients required hemodialysis and there were no sequel or deaths. There were 174 acute on chronic overdoses; hemodialysis was recommended in 9 patients but only 6 underwent hemodialysis; one patient died during hemodialysis but no other had sequel. There were 19 chronic poisonings; hemodialysis was recommended in 9 patients but only 2 had hemodialysis, a third patient underwent hemodialysis despite it not being recommended; one patient died without hemodialysis and one other had sequel after hemodialysis. No difference were observed between the groups for age, sex, type of poisoning (acute on chronic/chronic), levels (initial/peak/6 hours/extrapolated at 30 hours), time of presentation post-ingestion, presence of co-ingestants, symptoms and signs, Hansen and Amdisen grade, initial creatinine, time of recommendation to perform hemodialysis (daytime or nighttime), need to transfer patients to another centre to perform

hemodialysis, and outcome. Patients with acute on chronic poisoning that were not hemodialyzed had longer elimination half-life than those for whom hemodialysis was done even before hemodialysis was performed: 50.1 ± 13.6 h (n = 3) versus 12.9 ± 12.1 (n = 3) (p = 0.007), respectively. **Conclusion:** No difference was observed between patients for whom hemodialysis was done and those for whom it was recommended by PCC but not done. Despite the death of one patient clearly associated with voluntary withholding hemodialysis, sequel was not seen in that group. The indications for hemodialysis in lithium poisoning should be reconsidered to include only the more severe cases.

Introduction

Extracorporeal elimination of drugs is recommended for a limited numbers of compounds in poisoning situations, lithium is one of them. Over the years many criteria for performing hemodialysis in lithium poisoning have been suggested [Amdisen 1988, Bismuth et al. 1986, Dyson et al. 1987, Hansen and Amdisen 1978, Jaeger et al. 1985, 1993, Thomsen and Schou 1979]. These criteria have not been validated and there is no evidence that they modify outcome. In fact, most of these criteria are based on a study in which most patients had chronic poisoning, a situation not frequently encountered in a poison control centre population [Bailey and McGuigan 1999]. These different criteria usually consist of a combination of symp-

Received
December 8, 1999;
accepted in revised form
May 30, 2000

Correspondence to
Dr. B. Bailey
Department of
Pediatrics, Hôpital
Ste-Justine, 3175
Côte-Ste-Catherine,
Montréal, Québec,
H3C 1T5, Canada

toms, lithium levels and kinetics. Kinetic criteria are not always easily followed because lithium levels are not always readily available.

In addition, it has been demonstrated that criteria used as indications for performing hemodialysis are heterogeneous. In one case series of 14 hemodialyzed patients [Jaeger et al. 1993], anywhere from 1 to 10 patients would have been hemodialyzed if the other criteria had been used [Amdisen 1988, Bismuth et al. 1986, Dyson et al. 1987, Hansen and Amdisen 1978, Jaeger et al. 1985, Thomsen and Schou 1979]. The objectives of this report are to compare patients for whom hemodialysis was done for lithium poisoning with those for whom it was recommended by the poison control centre but not done, and to evaluate the effect of withholding hemodialysis on patient outcome.

Methods

All cases of lithium poisoning brought to the attention of the Ontario Regional Poison Information Centre from January 1 to December 31, 1996, were prospectively included in this case series. The Ontario Regional Poison Information Centre serves a population of 10 million in the province of Ontario and received an average of 250 poison-related calls/day.

When a case of lithium poisoning was identified by a Poison Information Specialist, one of the authors (BB) was contacted. The case was thereafter followed using a structured questionnaire until the patient became asymptomatic or was discharged, whichever came first. Information gathered included: age and weight, history of the poisoning (chronic therapy and dose taken, amount ingested, type of tablets, co-ingestants and time of ingestion), presenting symptoms, laboratory values (initial and subsequent lithium levels, creatinine), treatment used (activated charcoal, whole bowel irrigation, saline diuresis, hemodialysis) and outcome (mortality and morbidity).

An acute overdose was defined as a patient who ingested someone else's lithium tablets. A chronic poisoning was defined as no history of acute ingestion. Acute on chronic overdose was defined as the presence

of a history of acute ingestion in a patient who was being treated therapeutically with lithium, no effort was made to evaluate compliance with such treatment. Symptoms of the lithium poisoning were graded according to the classification of Hansen and Amdisen [1978]. Grade 0 were patients that were asymptomatic. Grade 1 were patients who had either nausea, vomiting, tremor, hyperreflexia, agitation, muscle weakness, or ataxia. Patients that were only drowsy were also considered to be grade 1. Grade 2 included patients with either stupor, rigidity, hypertonia or hypotension. Grade 3 were patients with coma, seizures, myoclonia and cardiovascular collapse. Creatinine was defined as abnormal if it was higher than the normal range in the hospital where the patient was treated.

Patients for whom hemodialysis was done were compared with those for whom it was recommended but not done in terms of clinical presentation, lithium elimination half-life, need for transfer to another centre for hemodialysis, and outcome (death or sequel or recovery) by analysis of variance, Chi-square or Fisher exact test, whichever applied. Elimination half-life of lithium were calculated using the method of least square regression before hemodialysis was performed. Elimination half-life were compared in each type of poisoning in patients for whom hemodialysis was done with those for whom it was recommended but not done by analysis of variance. The level of significance was set at 0.05.

Hemodialysis was generally recommended by the PCC according to the criteria: either coma, seizures, severe cardiac toxicity (3rd degree AV block, ventricular arrhythmias or hypotension) or creatinine higher than 200 mmol/l associated with a lithium level that is higher than 1.5 mmol/l in chronic poisoning or higher than 2.0 mmol/l in acute or acute on chronic overdose, or alteration of the level of consciousness, cardiac toxicity (prolonged QTc, ST segment or T waves abnormalities, or other arrhythmias) or creatinine higher than 150 mmol/l associated with a lithium level higher than 2.5 mmol/l in chronic poisoning or higher than 4 mmol/l in acute or acute on chronic overdose. Creatinine levels need to be assessed after a few hours of hydration. The criteria were based on a review of the literature.

Table 1. Clinical characteristics of patients for whom hemodialysis was done and those for whom it was recommended but not done.

| | Hemodialysis done (n = 8) | Hemodialysis not done (n = 9) | p value |
|-----------------------|------------------------------|----------------------------------|---------|
| Age (years) | 39.2 ± 9.3 | 54.8 ± 22.2 | 0.20 |
| Sex | 3 Male: 5 Female | 2 Male: 7 Female | 0.62 |
| Time of day* | 7 AM: 1 PM | 7 AM: 2 AM | 1.0 |
| Need to transfer | 5 No: 3 Yes | 5 No: 4 Yes | 1.0 |
| Type poisoning** | 6 A/C: 2 C | 3 A/C: 6 C | 0.15 |
| Timing post-ingestion | 5.4 ± 5.0 | 11.7 ± 9.4 | 0.28 |
| Co-ingestants | 3 No: 5 Yes | 7 No: 2 Yes | 0.34 |

* = AM from 0 h to 12 and PM from 12 to 24 h, ** A/C = acute on chronic poisoning
C = chronic poisoning

Table 2. Clinical symptoms of patients for whom hemodialysis was done and those for whom it was recommended but not done.

| | Hemodialysis done (n = 8) | Hemodialysis not done (n = 9) | p value |
|--------------------------|------------------------------|----------------------------------|---------|
| Neurologic symptoms | 8 | 9 | — |
| Cardiac symptoms | 4 | 4 | 0.80 |
| Hansen and Amdisen grade | 1 = 4 2 = 3 3 = 1 | 1 = 4 2 = 5 3 = 0 | NS* |

* = Non-significant

Table 3. Laboratory values in patients for whom hemodialysis was done and those for whom it was recommended but not done.

| | Hemodialysis done (n = 8) | Hemodialysis not done (n = 9) | p value |
|--------------------------|------------------------------|----------------------------------|---------|
| Initial [Li] (mmol/l) | 4.30 ± 1.99 | 2.71 ± 0.66 | 0.18 |
| Peak [Li] (mmol/l) | 4.70 ± 1.90 | 2.92 ± 0.79 | 0.39 |
| 6 hours [Li] (mmol/l) | 4.23 ± 2.27 | 2.53 ± 0.57 | 0.21 |
| 30 hours [Li] (mmol/l) | 2.41 ± 2.66 | 1.86 ± 0.91 | 0.50 |
| Creatinine [Li] (mmol/l) | 135 ± 79 | 162 ± 60 | 0.42 |

Table 4. Outcome in patients for whom hemodialysis was done and those for whom it was recommended but not done.

| | Hemodialysis done (n = 8) | Hemodialysis not done (n = 9) | p value |
|--------|------------------------------|----------------------------------|---------|
| Sequel | 1 | 0 | 0.47 |
| Death | 1 | 1 | 1.0 |

The number of patients that would have had hemodialysis using 5 published criteria were compared to what we suggested and

what was done [Amdisen 1988, Hansen and Amdisen 1978, Dyson et al. 1987, Thomsen and Schou 1979, Jaeger et al. 1985]. The comparison also mentioned if the criteria used would have hemodialyzed patients that died or had sequel.

Results

Over the study period, there were 205 cases of lithium poisoning brought to the attention of the poison control centre, 12 (6%) acute overdose, 174 (85%) acute on chronic and 19 (9%) chronic poisoning. Of all the cases, a total of 110 (54%) had lithium levels considered toxic (higher than 1.5 mmol/l).

In the 12 acute lithium overdoses, hemodialysis was not recommended or done for any patient and there were no sequel or deaths. In the 174 acute on chronic overdoses, hemodialysis was recommended in 9 patients but only 6 underwent hemodialysis. One patient died: she had a normal level of consciousness despite an initial lithium level of 8.92 mmol/l but she was ataxic and confused (grade 1), and died from pulmonary aspiration during hemodialysis. Also, beside this case, there were no sequelae in the acute on chronic overdoses. There were 19 chronic poisonings, hemodialysis was recommended in 8 patients but only 2 had hemodialysis, a third patient underwent hemodialysis despite not being recommended. One patient had residual numbness in the hands and high creatinine 4 months after the overdose despite normal creatinine prior to the overdose and hemodialysis. At follow-up done 6 months after the overdose, the numbness had resolved but the creatinine remained abnormal (240 mmol/l). One patient also died, hemodialysis was recommended but the treating physician decided not to perform hemodialysis after consultation with the family (the patient was in a basal vegetative state).

No differences were observed between the groups for age, sex, type of poisoning (acute on chronic/chronic), levels (initial/peak/6 hours/extrapolated at 30 hours), time of presentation post-ingestion, presence of co-ingestants, symptoms and signs, Hansen and Amdisen grade, initial creatinine, time of recommendation of hemodialysis (daytime or nighttime), need to transfer pa-

tients to another centre to perform hemodialysis, and outcome (Tables 1 to 4).

The patients for whom hemodialysis was suggested but not done had a lithium half-life of 40.9 ± 14.6 h ($n = 8$, 3 acute on chronic and 5 chronic poisoning) in comparison with 18.0 ± 14.2 h ($n = 4$, 3 acute on chronic and 1 chronic poisoning) pre-hemodialysis for those who were hemodialyzed ($p = 0.02$). Because the distribution of the poisoning type was different and the half-life was different according to the type of poisoning, we also compared half-life in only acute on chronic lithium poisoning: 50.1 ± 13.6 h ($n = 3$) in those not hemodialyzed compared to 12.9 ± 12.1 h ($n = 3$) pre-hemodialysis in those hemodialyzed ($p = 0.007$). A similar analysis for the chronic poisoning demonstrated lithium elimination half-life of 35.4 ± 13.4 h ($n = 5$) in those not hemodialyzed compared to 33.4 h ($n = 1$) pre-hemodialysis in the only patient hemodialyzed.

A total of 30, 25, 66, 24 and 13 patients would have had hemodialysis using the 5 published criteria [Amdisen 1988, Dyson et al. 1987, Hansen and Amdisen 1978, Jaeger et al. 1985, Thomsen and Schou 1979]. This is in comparison with 19 recommendations by poison control centre and only 10 performed (including one where it was not suggested). All criteria would have hemodialyzed the patients who died and the patient with the other sequel including ours.

Discussion

Despite the fact that hemodialysis is the most well documented technique for increasing lithium excretion, the indications to perform it have not been studied in large, controlled trials which clearly delineate the type of poisoning [Scharman 1997]. However, many criteria have been suggested [Amdisen 1988, Bismuth et al. 1986, Dyson et al. 1987, Hansen and Amdisen 1978, Jaeger et al. 1985, 1993, Thomsen and Schou 1979]. Hansen and Amdisen suggested that hemodialysis should be done if a lithium level less than 1 mmol/l cannot be achieved within 30 h, 21 out of these 23 patients had chronic poisonings [Hansen and Amdisen 1978]. Thomsen and Schou stated that hemodialysis should be used when a serum lithium level is higher

than 4 mmol/l or when cardiovascular symptoms are present or if a lithium level below 0.6 mmol/l cannot be achieved within 36 h [Thomsen and Schou 1979]. In 1988, Amdisen also stated that all patients with more than prodromal symptoms accompanied by increased serum lithium levels should undergo hemodialysis [Amdisen 1988]. Dyson et al. suggested that only patients with renal failure or those with rapidly rising or very high and potentially fatal serum lithium levels should be hemodialyzed [Dyson et al. 1987], this study involved 25 chronic poisoning cases and 43 deliberate self-poisonings [Dyson et al. 1987]. Finally, Jaeger et al. suggested criteria in one case report in 1985 [Jaeger et al. 1985]. Further definition of these criteria included clinical and kinetics criteria [Jaeger et al. 1993]. The clinical criteria were severe intoxication (grade 3 on the Hansen and Amdisen classification) with coma, convulsions or respiratory failure, progressive clinical deterioration, presence of underlying disease that may favor the development of complications, patients with acute on chronic or chronic poisoning. The kinetic criteria were impaired renal lithium excretion with increased serum concentration and half-life, continuing GI absorption with rising levels or continuing cellular diffusion, an amount of lithium expected to be removed by a 6-hour hemodialysis markedly higher than the 24-hour renal excretion. These recommendations were based on 2 acute overdoses, 7 acute on chronic overdoses and 5 chronic poisonings. Therefore, it appears that current recommendations for performing hemodialysis are not based on poison control centre study and, in most cases, are based on chronic poisoning. The present study aimed at evaluating patients in whom hemodialysis was done in comparison with those in whom it was suggested based on pre-defined criteria but not done.

The observed mortality and morbidity was low. When we compared both groups, there was no statistical difference. However, some of the variables we compared tended to be different between the groups. Patients in whom hemodialysis was performed tended to have higher levels (initial, 6 hours and extrapolated 30 hours) than those in whom we recommended dialysis but which was not done. This may have been caused by more acute on

chronic poisoning cases in those hemodialyzed than in those not hemodialyzed. However, the patients not hemodialyzed had an extrapolated 30-hour lithium level that was still higher than what was suggested by others, that is a level of 1 mmol/l at 30 hours. The higher extrapolated 30-hour lithium level was present in the dialyzed group despite faster elimination rate in that group versus the not dialyzed group. Considering that both groups had similar toxicity, this suggests that physicians tended to react to high lithium levels and not symptoms or decreased lithium excretion.

If we would have followed suggested criteria, more patients would have been hemodialyzed with the same results. This suggests that the published criteria are either too aggressive or they do not apply to poison control centre-based population. Criteria defining when to perform hemodialysis in lithium poisoning should be assessed by evaluating its effect on morbidity and mortality in a multicentric study as well as by an economic analysis before definitive criteria can be determined.

In conclusion, no difference was observed between patients for whom hemodialysis was done and those where it was recommended by PCC but not done. Despite the death of one patient clearly associated with voluntary withholding hemodialysis, other sequel was not seen in that group. In comparison with published criteria for when to perform hemodialysis in lithium poisoning, our recommendation yielded a different number of patients in which hemodialysis was suggested. Because patients in which no hemodialysis was done had apparently similar outcomes as those in which it was withheld, the indication for dialysis in lithium poisoning should be reconsidered to include only the more severe cases such as with the criteria suggested by Jaeger et al. [1993].

Acknowledgments

The authors would like to acknowledge all poison information specialists who identified cases of lithium poisoning and collected levels and Dr. Albert Jaeger for reviewing the manuscript.

Presented in part at the European Association of Poisons Centers and Clinical Toxicologists Scientific meeting, Zurich, Switzerland, March 1998.

Benoit Bailey was supported by a fellowship from the Canadian Society for Clinical Pharmacology.

References

- Amdisen A* 1988 Clinical features and management of lithium poisoning. *Med Toxicol* 3: 18-32
- Bailey B, McGuigan M* 1999 From a poison control centre perspective, how dangerous is lithium overdose? Proceedings of The European Congress of Clinical Toxicology, Oslo
- Bismuth C, Baud FJ, Buneaux F, duFretay XA* 1986 Toxicokinetics of lithium during a therapeutic overdose with renal failure. *J Toxicol Clin Toxicol* 24: 261-268
- Dyson EH, Simpson D, Prescott LF, Proudfoot AT* 1987 Self-poisoning and therapeutic intoxication with lithium. *Hum Toxicol* 6: 325-329
- Hansen HK, Amdisen A* 1978 Lithium intoxication. *Q J Med* 186: 123-144
- Jaeger A, Sauder P, Kopferschmitt J, Jaegle ML* 1985 Toxicokinetics of lithium intoxication treated by hemodialysis. *J Toxicol Clin Toxicol* 23: 501-517
- Jaeger A, Sauder P, Kopferschmitt J, Trisch L, Flesch F* 1993 When should dialysis be performed in lithium poisoning? A kinetic study in 14 cases of lithium poisoning. *Clin Toxicol* 31: 429-447
- Scharman EJ* 1997 Methods used to decrease lithium absorption or to enhance elimination. *J Toxicol Clin Toxicol* 35: 601-608
- Thomsen K, Schou M* 1979 The treatment of lithium poisoning. In: *Johnson FN (ed) Lithium Research and Therapy*. Academic Press, Orlando, FL, p 225