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Management of Lithium Toxicity

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Contents

Abstract

Lithium salts have been used in the prophylaxis and treatment of depression and bipolar disorder for >50 years. Lithium has a narrow therapeutic range, and several well characterised adverse effects limit the potential usefulness of higher doses. Acute ingestion in lithium-naive patients is generally associated with only short-lived exposure to high concentrations, due to extensive distribution of lithium throughout the total body water compartment. Conversely, chronic toxicity and acute-on-therapeutic ingestion are associated with prolonged exposure to higher tissue concentrations and, therefore, greater toxicity. Lithium toxicity may be life threatening, or result in persistent cognitive and neurological impairment. Therefore, enhanced lithium clearance has been explored as a means of minimising exposure to high tissue concentrations. Although haemodialysis is highly effective in removing circulating lithium, serum concentrations often rebound so repeated or prolonged treatment may be required. Continuous arteriovenous haemodiafiltration and continuous venovenous haemodiafiltration increase lithium clearance, albeit to a lesser extent than haemodialysis, and are more widely accessible. Haemodiafiltration sustained for >16 hours allows effective removal of total body lithium, thereby avoiding rebound effects. Enhanced elimination should be considered in patients at greatest risk of severe poisoning: namely those with chronic or acute-on-therapeutic toxicity, those with clinically significant features, and those with chronic toxicity whose serum lithium concentration is >2.5 mmol/L. The choice between haemodialysis and continuous haemodiafiltration techniques will depend on local accessibility and urgency of

enhancing lithium elimination. Further research is required to establish the potential benefits of assisted elimination on clinical outcome in patients with lithium poisoning.

1. Therapeutic Indications

In the early 1800s, lithium was proposed as a treatment for gout, based on the high *in vitro* solubility of urate in lithium-based solutions.[1,2] For many years, naturally occurring lithium-rich spring water was incorporated into remedies for gout and a wide variety of other ailments.[3] The eminent physician Alfred Baring Garrod (1819–1907) hypothesised that depression was a neurological manifestation of gout, so-called 'uric acid diathesis', which stimulated interest in the potential efficacy of lithium in this disorder.[4] However, the concentrations of lithium in naturally occurring spring water were low, and the quantities consumed were orders of magnitude lower than dosages that might now be expected to evoke a therapeutic effect.[5] A therapeutic role of lithium in psychiatry was established in the 1940s, and since then it has been used in prophylaxis and treatment of depression and bipolar disorder.[6] The mechanisms by which lithium exerts its therapeutic effects remain obscure. It is capable of interacting with a variety of neurotransmitter and cell signalling pathways, including phosphoinositide hydrolysis, adenylate cyclase, glycogen synthase kinase-3 beta and protein kinase C.[7] The impact of lithium on cytoskeletal phosphorylation is thought to evoke neuroplastic changes that lead to mood stabilisation.[7]

Regardless of its mechanism of actions, therapeutic responses to lithium are dose-dependent, reflected, in part, by accompanying serum concentrations.[8] Adverse effects of lithium are also dose-dependent and related to the duration of therapy. Characteristically, these include weight gain, tremor, polyuria, cognitive impairment and gastrointestinal disturbance. Recognised complications of long-term lithium treatment also include goitre, hypothyroidism, diabetes insipidus and renal failure. Impaired renal concentrating ability arises, at least in part, due to interference with adenylate cyclase-related intracellular signalling by vasopressin.[9] The extent to which chronic lithium treatment impairs renal function remains somewhat contentious. In a series of patients treated with lithium for up to 10 years, there was no apparent effect on renal function based on serum creatinine concentrations.[10] Conversely, others have found chronic lithium treatment to cause a slowly progressive decline in renal function, with an estimated interval of 20 years between initiation of therapy and end-stage renal disease.[11,12] The proposed mechanism of nephrotoxicity is drug-induced interstitial nephritis, and a number of specific histopathological features have been described, including cytoplasmic swelling, glycogen accumulation, dilated tubules and microcyst formation.[13,14]

In order to minimise the risk of adverse effects, therapeutic drug monitoring is normally required to maintain serum concentrations between 0.5–0.8 mmol/L, although a minority of patients require higher concentrations to achieve a clinical response.[8,15] In view of the increased risk of adverse effects associated with long-term therapy, treatment is normally constrained to no more than 5 years where possible. In certain patients who have demonstrated a significant response to lithium, maintenance treatment may be indicated for many years.

2. Toxicokinetics

2.1 Absorption

Oral administration of therapeutic lithium doses results in peak serum concentrations at 1–2 hours, and rapid and complete absorption from the gastrointestinal tract within 4–8 hours.[16,17] Extended-release formulations are associated with peak serum concentrations at 5–6 hours after administration.[18] Lithium carbonate has limited aqueous solubility and, therefore, ingestion of large quantities is expected to form concretions within the gastrointestinal tract. Therefore, in the setting of lithium overdose, gastrointestinal absorption may be significantly prolonged. This is particularly evident after ingestion of sustained-release preparations, which may be associated with peak serum concentrations at more than 48–72 hours after ingestion.[19-22]

2.2 Distribution

The volume of distribution of lithium has been reported to be between 0.6–0.9 L/kg, which corresponds closely with the total body water compartment.[23,24] Lithium pharmacokinetics are consistent with a multi-compartment model, including a rapid distribution phase between the intravascular and extracellular fluid compartments, slower elimination phase due to renal clearance, and gradual equilibration of concentrations between extracellular and intracellular compartments.[24-26] Lithium transportation is complex and, for example, distribution to the brain is delayed by around 24 hours compared with plasma.[27] Lithium is subject to active efflux from cerebrospinal fluid by arachadonic membranes and capillary endothelium, so that the ratio of cerebrospinal fluid to serum lithium concentrations during long-term treatment ranges between 0.25 and 0.6.[28-31] Several groups have examined erythro-

cyte lithium concentrations, as a surrogate marker of brain concentrations, but there is no consistent relationship and no correlation with the likelihood of response.[32,33] Erythrocyte concentrations have been proposed as a more informative marker of treatment compliance than serum lithium concentrations alone.[34] Brain lithium concentrations can be estimated using Li^7 magnetic resonance spectroscopy.[35] Although such techniques are not incorporated into routine clinical practice, they have demonstrated that peak brain lithium concentrations are delayed by at least several hours after peak serum concentrations.[35-37] These findings are directly relevant to lithium poisoning because they indicate the potential for delayed toxic features as tissue concentrations progressively increase.

2.3 Clearance

Lithium is a simple cation that is subject to negligible protein binding, and is cleared almost exclusively by renal excretion.[38] Around 80% of lithium filtered by the glomerulus is reabsorbed at the proximal convoluted tubule and, to a lesser extent, at the ascending limb of the loop of Henlé and collecting ducts.[39] In healthy people, renal clearance of lithium is around 25–35 mL/min, representing around one-quarter of the glomerular filtration rate.[40] Total body clearance is often delayed by on-going gastrointestinal absorption, especially in patients who have ingested large quantities of sustained-release lithium preparations.[41]

3. Patterns of Lithium Toxicity

Three broad patterns of lithium toxicity are recognised, each characterised by different toxicological and pharmacokinetic characteristics:

- acute toxicity arises in patients not previously receiving lithium;
- acute-on-therapeutic toxicity (often called acute-on-chronic toxicity) describes acute ingestion in the setting of lithium treatment;
- chronic toxicity is generally regarded as therapeutic misadventure and may arise from inadequate monitoring, inappropriately high target concentrations, or intercurrent illness.

Each of the three patterns are associated with different severity and duration of toxicity, based on the individual pharmacokinetic characteristics that determine tissue lithium concentrations. Lithium clearance may be substantially impaired in patients receiving chronic lithium treatment, particularly over a prolonged duration. Correspondingly, lithium half-life in patients with acute-on-therapeutic or chronic toxicity is significantly longer than that in patients with acute toxicity (50 vs 13 hours, respectively).[42] In patients with acute, acute-on-therapeutic and chronic lithium toxicity, serum lithium half-life has been reported as (mean ± standard deviation) 14 ± 7, 22 ± 9 and 29 ± 5 hours, respectively, and elsewhere 11.8, 20.9 (range 17.3–25.5 hours) and 32.2 hours (range 21.5–47.6 hours), respectively.[15,43] The plasma half-life and renal clearance of lithium in acute-on-therapeutic toxicity have been reported as 25.1 hours (range 19.0–26.9 hours) and 25.5 mL/min (range 20.3–32.6 mL/min), respectively, whereas in chronic toxicity these are 49.6 hours (36.5–79.4 hours) and 10.5 mL/min (range 6.0–19.8 mL/min), respectively.[44] Not surprisingly, therefore, there is wide variation in the reported lithium half-life in unselected patients with lithium poisoning, for example, cited as 8–45 hours.[45]

4. Clinical Features

Neurological features tend to predominate, including drowsiness, slurred speech, psychomotor slowing, bizarre behaviour, impaired memory and, in severe cases, seizures, coma and death.[46,47] Generalised polyneuropathy is a recognised feature, accompanied by an axonal pattern of toxicity,[48] and reversible choreoathetoid movement abnormalities have also been described.[49] The neurological manifestations of lithium toxicity may persist despite recovery from other effects and, therefore, lithium poisoning carries a risk of significant long-term morbidity and disability.[50-55] Lithium poisoning is associated with a number of distinctive histopathological abnormalities in cerebral and cerebellar tissue, both close to the time of intoxication and several years after recovery.[56-59] The presence of structural abnormalities supports the view that lithium toxicity is capable of evoking permanent neurological injury. However, it is difficult to establish causality from these reports due to the confounding effects of co-ingested drugs and pre-existing psychiatric illness.[56-58]

Clinical features of lithium toxicity may lag behind changes in serum lithium concentration due, at least in part, to delayed distribution into tissues.[60] Late toxicity is characteristic of the cardiovascular manifestations of lithium toxicity, which generally occur after neurological features are established.[17,61,62] Cardiac effects include rhythm disturbance, atrioventricular delay, heart block and a variety of non-specific ST-segment and T-wave abnormalities.[63,64] Acute renal failure is also recognised as a manifestation of lithium toxicity and may be sufficiently severe as to require renal replacement therapy.[65] Lithium ingestion by expectant mothers has been associated with cardiac fetal malformations.[66]

5. Poisoning Severity

In lithium-naive patients, peak serum concentrations decline rapidly due to dilution in a comparatively large volume of distribu-

tion. In contrast, acute-on-therapeutic and chronic lithium toxicity are generally associated with higher tissue concentrations and greater risk of toxicity. For example, although lithium enquiries to poisons centres most commonly concern acute toxicity (62%), only 11% of these were associated with moderate or severe acute poisoning; 19% of enquiries were about acute-on-therapeutic toxicity and 57% related to chronic toxicity.[67] Similar patterns have been observed in emergency departments where acute toxicity accounts for around 76% of cases, but moderate to severe features of poisoning are present in only 9% compared with 92% in patients with chronic toxicity.[43] Elsewhere, the clinical course after acute lithium toxicity has been described as generally uncomplicated compared with that of patients with chronic toxicity.[68,69]

Due to tissue saturation and impaired lithium clearance, patients with acute-on-therapeutic or chronic toxicity may be exposed to high lithium concentrations for more prolonged periods than patients with acute toxicity. Tissue lithium concentrations are likely to differ significantly between acute and chronic toxicity, which might not be readily discernable from serum measurements alone. Generally, the correlation between serum lithium concentrations and severity of symptoms is poor. One study found that in chronic lithium toxicity, serum lithium concentrations were higher in patients with neurological features than in those without significant features (2.3 vs 1.6 mmol/L, respectively).[70] More importantly, the strongest predictors of severe toxicity are reported as diabetes insipidus, age >50 years, hypothyroidism and impaired renal function, although the latter was of borderline statistical significance.[70] These findings underpin the importance of the duration and extent of lithium exposure in predicting the likelihood of clinically relevant toxic effects.

A classification system has been proposed by Hansen and Amdisen[71] to indicate the severity of intoxication, particularly in patients with chronic toxicity. This classification has not yet been validated prognostically, although it emphasises the importance of some neurological features.

6. Management

6.1 Induced Emesis

Induced emesis is associated with an unacceptably high risk of adverse effects. Furthermore, there is a lack of evidence of efficacy or improved clinical outcome in patients who may have ingested any one of a number of poisons, including lithium. Therefore, induced emesis (e.g. by syrup of ipecacuanha) should be avoided.[72]

6.2 Gastric Lavage

In a small series of patients, gastric lavage was associated with highly variable recovery of lithium; mean 93.9 mmol (range 0.4–530 mmol), equivalent to 18.0% (range 0.3–65.5%) of all lithium recovered during the total observation period.[17] In a patient who ingested lithium carbonate and trichobezoar, serum lithium concentrations persisted at >4 mmol/L for 85 hours post-ingestion due to prolonged gastrointestinal absorption. Endoscopic lavage and aspiration of stomach contents was followed by a rapid decline in serum lithium concentrations.[73] These limited data do not allow firm conclusions to be drawn regarding the effectiveness of gastric lavage after lithium ingestion, and there is no satisfactory evidence of improved outcome.[74]

6.3 Whole Bowel Irrigation

Whole bowel irrigation is capable of allowing reduced gastrointestinal absorption of lithium carbonate by, for example, administration of polyethylene glycol 10L at 2 L/h, 1 hour after a therapeutic lithium dose in healthy subjects.[75] Despite a possible reduction in drug absorption, there are no data from controlled clinical trials to suggest that whole bowel irrigation is associated with improved clinical outcome.[76] Lithium carbonate is sparingly soluble in aqueous media and, at least in theory, enteral fluid administration might increase the solubility of salt concretions and hasten lithium absorption.

6.4 Gut Decontamination

Activated charcoal does not adsorb lithium to any significant extent, as evidenced during *in vitro* studies incorporating simulated gastric pH conditions.[77] A potentially effective alternative is sodium polystyrene sulfonate (Kayexalate®),[1] a cation exchange resin that is capable of binding lithium *in vitro* in a dose-dependent manner.[78] Whereas activated charcoal had no effect on gastrointestinal absorption of lithium in mice, sodium polystyrene sulfonate reduced absorption in a dose-dependent manner, and the effect was enhanced by repeated administration.[79,80] The mechanism of action of sodium polystyrene sulfonate is complex because it is also capable of enhancing elimination of parenterally administered lithium, suggesting that it might directly or indirectly influence renal handling of lithium.[81] In healthy people, sodium polystyrene sulfonate delays the time of peak lithium concentrations by around 2 hours, and reduces overall lithium exposure by 11–48%, as determined by the area under concentration-time curves.[82-84] In a patient with acute lithium toxicity, sodium polystyrene sulfonate 150g did not cause any significant adverse

1 The use of trade names is for product identification purposes only and does not imply endorsement.

effects, and the reported lithium half-life was 12 hours.[85] Despite promising pre-clinical and early clinical data, insufficient evidence exists to support the use of sodium polystyrene sulfonate, and further work is required to establish its role in poisoned patients.

Bentonite is an absorbent that has been explored as a means of reducing gastrointestinal absorption of a number of agents, for example paraquat.[86] Bentonite adsorbs lithium carbonate *in vitro*, although its effect on gastrointestinal absorption has not been evaluated in a clinical setting.[87]

6.5 Forced Diuresis

Administration of large volumes of isotonic sodium chloride to enhance urinary sodium excretion had no significant effect on fractional lithium clearance; lithium renal clearance was 26.5 and 29.2 mmol/day before and during treatment, respectively.[71] Furthermore, saline administration may be complicated by development of hypernatraemia in patients with lithium toxicity.[71] Loop diuretics may enhance fractional lithium clearance in healthy people, although the underlying mechanism is unclear.[88] However, significant discrepancies exist between healthy people and patients with lithium toxicity, perhaps due to differences in renal function, hydration status and sodium homeostasis.[89] Forced diuresis using furosemide 60mg and large volumes of intravenous isotonic crystalloids (5–7 L/day for 3 days) was claimed to increase lithium clearance.[90] However, the presented data were insufficient to conclude benefits greater than might be expected from correction of hydration alone.

'Forced alkaline diuresis', by means of intravenous crystalloids to maintain urine pH ≥7.0, has been suggested to improve lithium clearance, based on an observed serum half-life of 13 hours, although this half-life does not differ substantially from values reported in patients treated with conservative measures alone.[91] Lithium clearance during forced diuresis has been reported as around 22 mL/min,[92,93] and elsewhere has been deemed ineffective as a means of enhancing lithium elimination.[40] A recent observational study found that neither serum lithium concentrations nor clinical outcomes were different between patients treated by forced diuresis and those treated by correction of electrolyte and hydration status.[94]

In one report, systemic administration of dopamine 2 μg/kg/min appeared to increase renal clearance of lithium clearance.[95] However, on closer inspection, the data suggest that fractional lithium excretion was actually unchanged.

6.6 Haemodialysis

In a series of 14 patients with lithium toxicity, spontaneous lithium kinetics showed a mean half-life of 23 hours (range 9–37 hours) and renal clearance of 17.2 mL/min (range 0.8–22.3 mL/min), whereas in three patients haemodialysis was accompanied by a serum half-life of 4.8 hours (range 3.6–5.7 hours) and dialysis clearance 86.7 mL/min (range 63.2–114.4 mL/min).[23] Haemodialysis eliminated 68.6 mmol (range 48.4–92.3 mmol) lithium, representing 33.3% (range 17.2–39.6%) of the total lithium recovered, whereas 123.7 mmol (44.3–239.0 mmol) was eliminated by renal excretion between the beginning of the first and the end of the last haemodialysis.[23] Elsewhere, acute lithium toxicity was associated with renal clearance 13–30 mL/min; however, haemodialysis gave plasma clearance of 89–105 mL/min. Despite a substantially shortened elimination half-life (2.3–4.8 hours) during haemodialysis, the overall half-life was less impressive when rebound serum concentrations were considered (6.2–12.0 hours).[40] These data indicate that despite haemodialysis being highly efficient at reducing circulating lithium concentrations, it is less effective at removing lithium from the intracellular compartment (figure 1), and repeated courses are required, as reported elsewhere.[60,65]

The effects of acetate dialysate and bicarbonate dialysate were compared during sequential haemodialysis in a patient with acute-on-therapeutic lithium toxicity; lithium clearance during dialysis was 111 mL/min for both solutions.[97] The authors concluded that bicarbonate dialysate may be more effective than acetate dialysate for clearing extracellular lithium, but an inadequate interval between treatments meant that the pharmacokinetic analysis was confounded by anticipated rebound effects.

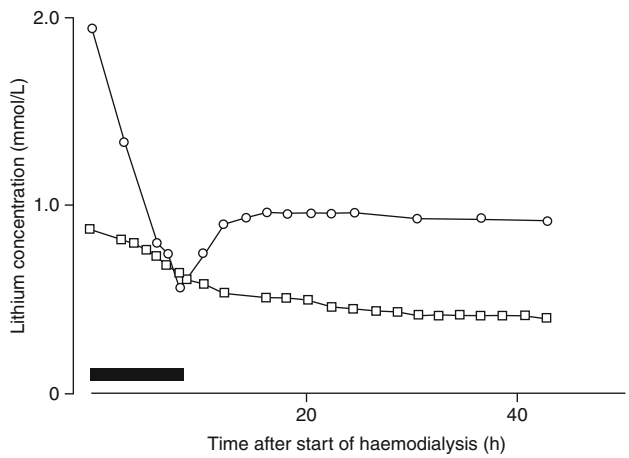

Fig. 1. Haemodialysis causes a dramatic reduction of serum lithium concentrations followed by rebound (open circles), whereas effects on cerebrospinal fluid concentrations (open squares) are less pronounced (reproduced from Amdisen,[96] with permission).

In a patient with severe lithium toxicity, haemodialysis for 17.5 hours decreased serum concentration from 14.6 to 6.0 mmol/L and three further sessions were required to achieve a concentration <1.5 mmol/L. Rebound occurred between each session and the patient did not regain consciousness until several days after concentrations <1.5 mmol/L had been achieved.[98] The patient developed significant hypotension during haemodialysis and required inotrope administration to maintain systemic blood pressure. He was subsequently diagnosed with myocardial infarction, despite normal coronary arteriography, and this was attributed to lithium toxicity. Nonetheless, the case illustrates the potential for haemodialysis to cause significant haemodynamic disturbance, particularly in patients with established vascular disease.

In certain patients, neurological adverse effects have been reported to coincide with declining serum concentrations during therapeutic use.[99] The same author also reports a close temporal relationship between falling serum lithium concentrations during haemodialysis and deterioration of cognitive impairment.[100] These observations raise the possibility that overly rapid correction of serum lithium might be detrimental. One proposed mechanism is that rapid removal of intracellular lithium might be followed by a compensatory influx of sodium ions; this is analogous to the rapid influx of sodium ions during correction of hyponatraemia, which is thought to underpin central pontine myelinolysis.[101] Evidence of a causal link is lacking, but the findings suggest that caution is required in determining the optimum rate of lithium removal.[102]

Haemodialysis allows highly effective lithium clearance of around 100–150 mL/min and has been advocated for patients with severe toxic features, or those with high serum lithium concentrations, or lithium concentrations that are declining slowly.[71] Original studies supported the need for repeated haemodialysis sessions or prolonged treatment for at least 10–12 hours to allow adequate removal of lithium, and a suggested guide to determining the adequacy of haemodialysis was attainment of serum lithium concentrations <1.0 mmol/L 6–8 hours after dialysis, based on the prevailing therapeutic range rather than outcome measures.[71]

There is little evidence of the impact of haemodialysis on outcome measures in patients with lithium toxicity. Comparison between haemodialysis and conservative measures in two patients with acute-on-therapeutic lithium toxicity found that haemodialysis allowed more efficient lithium clearance than renal excretion alone (108 vs 10.8 mL/min), and 84 mmol lithium was removed by haemodialysis 65.6% of the total recovered, although the duration of haemodialysis was not reported.[103] However, toxicity and duration of neurological symptoms was similar in both patients. Follow-up of enquiries about lithium toxicity referred to the Ontario Poisons Center showed that haemodialysis was implemented in six of nine patients with acute-on-therapeutic toxicity, and three of nine patients with chronic toxicity in whom it had been recommended.[42] Clinical outcomes were similar between those who received haemodialysis and those who did not in each group, although these data are potentially confounded by patient selection bias by the treating physician.

6.7 Continuous Arteriovenous Haemodiafiltration and Continuous Venovenous Haemodiafiltration

Continuous arteriovenous haemodiafiltration (CAVHD) was described around 20 years ago.[104] Experience of CAVHD in lithium poisoning was first reported in a patient in whom access to haemodialysis was delayed.[105] Treatment for 14 hours, at a dialysate flow rate of 1 L/h, was associated with a fall in serum lithium concentrations from 5.1 to 1.1 mmol/L and clinical improvement. Serum concentrations rebounded to 2 mmol/L 17 hours later, and CAVHD was recommenced. Lithium clearance by CAVHD was reported as 20.5 mL/min.

CAVHD and continuous venovenous haemodiafiltration (CVVHD) were examined in a series of seven patients, in whom lithium clearance was estimated between 4–15 times. CAVHD in five patients, at dialysate flow-rate of 4 L/h for 22 hours (range 15–35 hours), was associated with dialysis lithium clearance of 42.5 mL/min (range 27.6–55.6 mL/min), total lithium clearance of 53.3 mL/min (range 35.5–72.3 mL/min) and lithium removal of 129 mmol (range 43–170 mmol). CVVHD in one patient, at dialysate flow rate of 2 L/h for 42 hours, was associated with dialysis lithium clearance of 61.9 mL/min, overall lithium clearance of 66.3 mL/min and lithium removal of 163 mmol; CVVHD in one patient, at dialysate flow rate of 1 L/h for 44 hours, was associated with dialysis lithium clearance of 48.4 mL/min, overall lithium clearance of 50.8 mL/min and lithium removal of 86 mmol.[106] This series confirmed the effectiveness of continuous renal replacement therapy as a means of substantially enhancing lithium clearance, whilst avoiding rebound effects. Despite this, the study design did not address whether treatment had any direct impact on outcome measures. Other data support the use of continuous venovenous haemofiltration with high dialysate flow rates over a prolonged period, which gives comparable lithium clearance to CAVHD, and also diminishes the risk of haemodynamic instability that might be encountered during haemodialysis.[107]

Existing data support the role of prolonged treatment with CAVHD and CVVHD as a means of allowing high solute clearance and effectively enhancing lithium clearance. These techniques may exert fewer haemodynamic effects than haemodialysis, so that they can be implemented over a sustained period,

although this is somewhat controversial.[108] Continuous renal replacement techniques, in particular CAVHD, are increasingly accessible in critical care areas and their implementation does not normally require haemodialysis-trained staff. Therefore, initiation of CAVHD might be expected to impose fewer delays than required for implementation of haemodialysis, but evidence to support this is not available.

6.8 Peritoneal Dialysis

Peritoneal dialysis is associated with lithium clearance of 8.0–10.6 mL/min and, when sustained over a 12-hour period, causes a 40% decrease in serum lithium concentrations.[109] Similar lithium clearance values, 13–15 mL/min, have been reported elsewhere and suggest that peritoneal dialysis is capable of enhancing lithium clearance, but to a lesser extent than haemodialysis or CAVHD.[110] Therefore, peritoneal dialysis may be considered where there may be unavoidable delays to instituting haemodialysis or CAVHD, or if the latter methods are unsuitable for other reasons.

7. Critique of Treatment Modalities

Gastric lavage may allow recovery of clinically significant quantities of lithium, and should be considered for patients who have ingested potentially toxic quantities of lithium within 1 hour. Whole bowel irrigation may reduce gastrointestinal absorption of lithium, and should be considered for patients in whom there is a significant risk of prolonged absorption, for example, after ingestion of large quantities of sustained-release preparations. Whilst both gastric lavage and whole bowel irrigation are capable of reducing lithium absorption in selected patients, further work is required to establish whether these techniques have any effect on poisoning severity or clinical outcome.

Haemodialysis provides a highly effective means of reducing circulating lithium concentrations. However, an important rate-limiting factor in removing lithium from the body is diffusion between the intracellular and extracellular compartments. Haemodialysis should be considered in patients in whom serum lithium concentrations are high, or rising, because there is an opportunity to effectively clear high amounts of lithium from the circulation.[103] There are too few data to determine whether very rapid lowering of the serum lithium concentration is advantageous, ineffective, or even detrimental. Furthermore, the advantages of rapid clearance of lithium by haemodialysis, compared with continuous renal replacement therapy, might be negated by the need for sustained or repeated treatments to compensate for rebound effects.

Both CAVHD and CVVHD increase lithium clearance, albeit less rapidly and extensively than haemodialysis. Continuous renal replacement for at least 24 hours allows sustained and continuous clearance of total body lithium, whilst avoiding rebound of serum concentrations after treatment cessation. Despite these observations, little data exist to inform the likely impact of either treatment on outcome. Moreover, existing data do not permit direct comparison of haemodialysis and continuous renal replacement techniques.

Few evidence-based data exist to guide the optimal initiation and duration of dialysis. In patients with chronic lithium toxicity, concentrations between 1.5–2.5 mmol/L are associated with mild or moderate symptoms, concentrations between 2.5–3.5 mmol/L are associated with severe toxicity, and concentrations >3.5 mmol/L may be life threatening.[71] On this basis, it would seem rational to consider enhanced elimination in patients at greatest risk of severe poisoning, namely those with chronic toxicity whose serum lithium concentration is >2.5 mmol/L. However, others have found less good correlation between concentrations and severity in chronic toxicity and lack of any correlation in patients with acute or acute-on-therapeutic toxicity.[111]

Amdisen[96] had recommended haemodialysis for patients with serum lithium concentrations >1.4 mmol/L at 12 hours, whereas others[112] have suggested it is necessary only if the patient has renal impairment or clinical features of toxicity. One group has advocated extrapolation of the semi-logarithmic concentration time curve to the time when lithium concentrations will have decreased to 0.6 mmol/L, in order to identify those at greatest risk of prolonged exposure to high concentrations.[113] The need for dialysis is unlikely to be determined from serum lithium concentrations alone, and it has been suggested that both clinical features and kinetic data within 12 hours of hospital admission are important.[23] The decision to implement dialysis should be based on the presence of severe clinical toxicity, or the likelihood of severe features based on the pattern of poisoning, dose and timing of lithium ingestion, and serum lithium concentrations.

The endpoint of dialysis techniques is substantially reduced tissue lithium concentrations. Given the difficulty in extrapolating between serum and tissue lithium concentrations, the endpoint might be better ascertained by clinical assessment (e.g. sustained improvement in neurological state). Adequate tissue clearance of lithium is accompanied by a persistent reduction of serum concentrations, which might also be indicated by lack of rebound 6–8 hours after stopping dialysis.[71] Due to the inadequacy of serum concentrations to predict toxicity, cerebrospinal fluid concentrations of <0.1 mmol/L have been proposed as a more reflective endpoint for treatment; however, again, this is not based on evidence of improved outcome.[60]

8. Conclusions

Acute lithium poisoning results in a higher number of poisons centre enquiries and emergency department attendances than chronic poisoning, but toxic effects are generally milder than encountered in the setting of chronic toxicity. Both haemodialysis and continuous renal replacement are capable of reducing overall exposure to high lithium concentrations; however, there is little constructive evidence of improved clinical outcome or direct comparative data between these modalities. Enhanced elimination should be considered in patients at greatest risk of severe poisoning: namely those with chronic or acute-on-therapeutic toxicity, those with clinically significant features, and those with chronic toxicity whose serum lithium concentration is >2.5 mmol/L. The choice between haemodialysis and haemofiltration will depend on local accessibility of either technique, the urgency of lithium lowering and haemodynamic status of the patient. Further research is required to define the role of assisted elimination techniques on short- and long-term outcome measures in patients with lithium toxicity.

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