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In Vitro Adsorption of Lithium by Bentonite

R Ponampalam, E J Otten

ABSTRACT

Background: Lithium poisoning is currently managed using a combination of supportive care and urgent haemodialysis in severe cases. Activated charcoal as a gut decontaminant has been found to be ineffective. The use of Sodium Polystyrene Sulphonate (SPS) as an adsorbent has been found to be effective in some studies. However, there have been case reports of gut necrosis and perforation occurring when SPS was used for the treatment of hyperkalaemia in post operative patients or patients with renal failure. Bentonite is a known adsorbent that has been used in the management of paraquat poisonings. The purpose of this study was to determine the ability of bentonite to adsorb lithium.

Method: 4.5 g of lithium carbonate was dissolved in 1.5 L of deionised water to form the stock solution. 50 mL aliquots of this stock solution were added to 50 mL of either distilled deionised water (pH 7) or simulated gastric fluid (pH 1.2). Bentonite of either 0.75, 1.5 or 4.5 g was then added to simulate 5:1, 10:1 and 30:1 ratio of adsorbent-to-drug. Controls were made with no bentonite added. The resulting mixture was placed on a shaker for five minutes before being filtered. The filtrate was diluted and batch analysed for lithium using atomic absorption spectrophotometry.

Results: Bentonite decreased the concentration of lithium recovered from the filtrate by 20.55% in deionised water compared to 48.09% in simulated gastric fluid at a bentonite:lithium ratio of 30:1 (p value 0.005).

Conclusion: This study shows that bentonite is an effective adsorbent for lithium. The effect is enhanced in simulated gastric fluid. *In vivo* studies are being planned for clinical correlation.

Keywords: Lithium poisoning, Bentonite, Adsorbent

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INTRODUCTION

Lithium is a drug commonly used in the treatment of manic depressive illness creating the potential for accidental and intentional overdose. This, combined with the narrow therapeutic index of lithium, makes lithium toxicity a major concern.

In Singapore, the incidence of lithium poisoning is unknown. However, in the United States of America, the American Association of Poison Control Centers (AAPCC) collates toxic exposures from inputs received from regional poison centers into a centralised database. According, to the AAPCC's Annual Report of the Toxic Exposure Surveillance System (TESS) which is derived from this database, there were just over two million toxic exposures reported in 1998[1]. Although lithium exposures accounted for 4486 cases, there were five deaths and 1105 moderate to severe poisonings amongst these cases. It is evident that improvements in the management of this latter category of patients are needed.

The treatment of severe lithium overdose involves, first of all, supportive care, including fluid resuscitation and haemodialysis, in severe overdoses[2,3] Gut decontamination techniques include gastric lavage in early case presentations and whole bowel irrigation for ingestion's involving sustained release formulations. Activated charcoal, a universal adsorbent for many toxins, has been found to be ineffective for lithium poisoning[4,5]. Alternatives such as sodium polystyrene sulfonate (SPS) or Resonium has been shown to be effective in adsorbing lithium, thus reducing its bioavailability[6-13]. SPS however has been associated with gut necrosis and perforation, especially in the treatment of hyperkalemia in renal failure or post operative patients[14-17]. It is suspected that the sorbitol in the SPS mixture may be responsible for this effect. Additional risk factors are potential for hypokalaemia[18] as well as hypernatraemia and fluid overload, although the increased sodium load may enhance the renal clearance of lithium[9].

Bentonite is a long forgotten adsorbent. It was used in paraquat poisoning as a gastric decontaminant but has largely been replaced by activated charcoal.

Table I. Concentration of lithium recovered from filtrate.

Bentonite (grams) (bentonite: lithium ratio)	Mean lithium concentrations recovered (ng/ml) (+/- SD)		Mean lithium adsorbed compared to control (ng/ml)		t-test for paired differences of means						
	DI[Δ] (N*= 3)	SGF[ɜ] (N*= 3)	DI[Δ] (N*=3)	SGF[ɜ] (N*=3)	Mean Diff.	SD	SE	CI 95%	t	df	Sig. (2 tailed)
0 (control)	434.02 (+/- 15.49)	455.73 (+/-10.08)	0	0							
0.75 (5:1)	423.16 (+/- 4.11)	341.88 (+/- 4.30)	10.89 (SD = 18.01)	113.85 (SD= 5.78)	-102.96	12.32	7.11	-133.56, -72.36	-14.48	2	<.005
1.5 (10:1)	378.08 (+/- 2.48)	265.87 (+/- 5.92)	55.97 (SD = 17.99)	189.86 (SD= 15.74)	-133.89	2.34	1.35	-139.71, -128.08	-99.06	2	<.001
4.5 (30:1)	344.84 (+/- 4.30)	236.58 (+/- 7.14)	89.20 (SD = 16.87)	228.15 (SD= 17.22)	-138.95	16.79	9.69	-180.65, -97.25	-14.34	2	<.005

* Number of experiments in each group

[Δ] DI = Deionised water

[ɜ] SGF = Simulated gastric fluid

Bentonite, like SPS, is a cation exchange resin, which has found applications in industry as an agent capable of removing cation impurities.

The purpose of this study was to investigate the *in vitro* adsorption of lithium by bentonite.

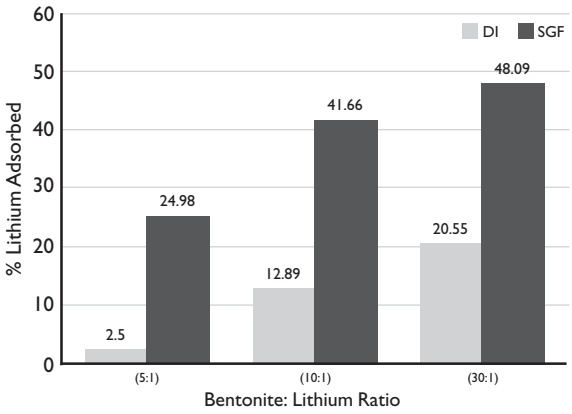
MATERIALS AND METHODS

Experimental methodology as carried out by Fran Favin et al[4] was followed except for starting concentrations of reagents which were halved to accommodate the greater sensitivity of atomic absorption spectrophotometry (AAS) used in the final quantification of the samples.

A stock solution of lithium carbonate was made by dissolving 4.5 g of lithium carbonate (ACS reagent grade, Sigma-Aldrich Corporation, St Louis, MO) in 1.5 L of deionised water. Aliquots of the stock solution 50 mL were added to 50 mL of deionised water (pH 7) or simulated gastric fluid (USP XXXIII, pH 1.2). Bentonite (Sigma-Aldrich Corporation, St Louis, MO) 0.75, 1.5 or 4.5 g was then added to make adsorbent: drug ratios of 5:1, 10:1 and 30:1 respectively. Controls were made with no bentonite added. The resulting mixture was shaken for five minutes at room temperature before paper filtration. The filtrate was then diluted in distilled deionised water and batch analysed for lithium by AAS (Perkin Elmer 380 Atomic Absorption Spectrophotometer, Serial number 90428). Spectrophotometer readings (absorbance at 670.8 nm wave length as recommended for lithium) were converted to concentrations by using a standard curve from photometer readings generated by standard reagents of known concentrations.

Statistical analysis of the data was carried out using analysis of variances (GLM repeated measures).

Fig.1 Lithium absorbed by bentonite compared to controls[@].



[@] % Lithium adsorbed by bentonite compared to controls = (mean concentration of lithium recovered at respective controls for deionised water or simulated gastric fluid) subtract (mean concentration of lithium recovered at bentonite levels 0.75, 1.5 or 4.5) divided by mean concentration of lithium recovered in the respective controls multiplied by 100.

RESULTS

The mean differences between the concentrations of lithium at increasing amounts of bentonite and between deionised water and simulated gastric fluid were statistically significant at $p<0.005$, using the paired samples T test for the differences in means (Table I). It is noted that as the bentonite-to-lithium ratio increases, there is decreasing recovery of free lithium suggesting possible adsorption of lithium by bentonite.

Repeated measures analysis of variance using the statistical model with GLM (repeated measures) was performed using SPSS version 10. This test was done to determine the statistical significance in the differences in adsorption of lithium by bentonite in the two experimental arms as well as with increasing bentonite

to lithium ratios. The differences in the adsorption of lithium by bentonite between the two experimental arms comprising deionised water and simulated gastric fluid environment were noted to be statistically significant at $p<0.001$. This suggests that the different experimental solutions could have contributed to the different amounts of lithium adsorbed. Therefore, it is likely that bentonite is more effective in adsorbing lithium in a simulated gastric fluid environment.

Similarly, the differences in the adsorption of lithium at increasing concentration ratios of bentonite to lithium (5:1, 10:1 and 30:1) in each experimental arm was noted to be statistically significant at $p<0.001$. This suggests that increasing amounts of bentonite could have resulted in increasing extraction of lithium from the experimental solutions.

At the clinically relevant ratio of adsorbent-to-drug of 10:1, there is a three fold increase in effectiveness of the bentonite in simulated gastric fluid compared to deionized water (Fig. 1) ($p<0.001$).

DISCUSSION

Lithium is widely used in the treatment of manic depressive disorders. Toxicity from excessive ingestion is severe including cardiovascular conduction abnormalities, renal damage and central nervous system sequelae.

The management of lithium intoxication includes measures to decrease lithium absorption and increase lithium elimination. The latter includes forced saline diuresis, continuous arteriovenous haemodiafiltration, low dose dopamine infusion, intravenous aminophylline and haemodialysis.

Methods to decrease lithium absorption in acute overdoses include gastric decontamination techniques such as gastric lavage, whole bowel irrigation (WBI) for sustained release preparations and the use of adsorbents such as sodium polystyrene sulfonate (SPS).

The role of adsorbents in lithium overdoses has been investigated extensively. Activated charcoal (AC), a universal adsorbent for many toxins, was found to be ineffective as an adsorbent for lithium in an animal experiment[4,5]. AC has a higher affinity for non-ionised particles and hence its ability to adsorb a strong cation like lithium may be limited.

Sodium polystyrene sulfonate (SPS) may be an adsorbent of choice for lithium based on its efficacy in several *in vitro* and *in vivo* studies[6-13]. In animal studies, it was noted that large doses, 5 to 10 g/kg, of SPS were needed to produce an effect. This extrapolates to 700 g for a 70 kg patient, but a case report of SPS for the treatment of acute-on-chronic lithium overdose showed a much lower dose of 150 g to be effective[9]. The lowest effective dose of SPS is yet to be derived. SPS in itself is not an innocuous agent. There are reports of hypernatraemia with fluid overload, hypokalaemia, and intestinal ulcers and necrosis when SPS is given for correction of hyperkalaemia at standard therapeutic doses[14-18]. However, studies by Lillemoe et al[17] using either SPS alone (no sorbitol) or sorbitol enemas without SPS in uraemic and non uraemic rats showed that it was probably the sorbitol rather than the SPS that was responsible for the colonic ulceration. Given the risk and cost of SPS, alternative adsorbents for lithium merit investigation.

Bentonite, like SPS, is a cation exchange resin, long used in the oil refining industry as an adsorbent for impurities including cations. Lithium is a strongly basic cation that is completely ionised in solution, thus making it readily available for exchange. These properties of both adsorbent and drug could explain the effectiveness of lithium adsorption by bentonite. The efficacy of bentonite at a clinically feasible ratio of 10:1 (adsorbent: drug) was 12.89% in water and 41.66% in SGF. The enhanced adsorption in an acidic solution may predict in vivo efficacy although agents that lower gastric acidity, such as antacids, H2 blockers and food may reduce adsorption. The binding capacity of bentonite may also be reduced by the potassium ions of gastric fluid. There is also a possibility of desorption of lithium from bentonite as the lithium-bentonite complex enters into the alkaline medium of the small intestine. These effects, as well as that of body temperature, need to be addressed in future studies.

The safety profile of bentonite also requires additional consideration. Patients suffering from geophagia and the chronic ingestion of clay may present with profound hypokalemia and weakness, polymyositis with elevated creatine kinase, and iron deficiency anemia[19-21]. The responses to chronic ingestion may not be relevant to the single, acute, therapeutic doses of bentonite.

CONCLUSION

This study shows that bentonite is an effective adsorbent for lithium. The effect is enhanced in simulated gastric fluid. *In vivo* studies are being planned for clinical correlation.

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