Pharmacokinetics and toxic effects of lithium chloride after intravenous administration in conscious horses

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Objective—To determine the pharmacokinetics and toxic effects associated with IV administration of lithium chloride (LiCl) to conscious healthy horses.

Animals—6 healthy Standardbred horses.

Procedure—Twenty 3-mmol boluses of LiCl (0.15 mmol/L) were injected IV at 3-minute intervals (total dose, 60 mmol) during a 1-hour period. Blood samples for measurement of serum lithium concentrations were collected before injection and up to 24 hours after injection. Behavioral and systemic toxic effects of LiCl were also assessed.

Results—Lithium elimination could best be described by a 3-compartment model for 5 of the 6 horses. Mean peak serum concentration was 0.561 mmol/L (range, 0.529 to 0.613 mmol/L), with actual measured mean serum value of 0.575 mmol/L (range, 0.52 to 0.67 mmol/L) at 2.5 minutes after administration of the last bolus. Half-life was 43.5 hours (range, 32 to 84 hours), and after 24 hours, mean serum lithium concentration was 0.13 ± 0.05 mmol/L (range, 0.07 to 0.21 mmol/L). The 60-mmol dose of LiCl did not produce significant differences in any measured hematologic or biochemical variables, gastrointestinal motility, or ECG variables evaluated during the study period.

Conclusions and Clinical Relevance—Distribution of lithium best fit a 3-compartment model, and clearance of the electrolyte was slow. Healthy horses remained unaffected by LiCl at doses that exceeded those required for determination of cardiac output. Peak serum concentrations were less than steady-state serum concentrations that reportedly cause toxic effects in other species. (*Am J Vet Res* 2001; 62:1387–1392)

Measurement of cardiac output that uses lithium chloride as an indicator has been described in the human literature[1,2] and compared with measurement of cardiac output by thermodilution in swine,[3] humans,[4] dogs,[a] and horses.[5] On the basis of these studies, it appears that cardiac output measured via lithium chloride dilution is a safe, simple, and accurate technique that yields results at least as accurate as those for bolus thermodilution. Historically, cardiac output measurements in horses have been performed by use of dye dilution or thermodilution.[6-8] More recently, transesophageal Doppler echocardiography has been used in anesthetized horses.[9] Dye dilution is expensive and cumbersome, and the equipment required for transesophageal Doppler echocardiography is specialized and expensive. Although the thermodilution method has been widely used for research investigations for the past 2 decades, the technique requires invasive insertion of a catheter in a pulmonary artery and the inherent risks associated with such catheterization,[b] making it difficult to use this method in a clinical setting. Lithium chloride dilution involves injection of lithium chloride into a central vein and subsequent detection in blood samples obtained from a peripheral artery, using a lithium selective electrode. The method offers a number of possible advantages for estimation of cardiac output in a clinical setting.[5]

Lithium chloride has been used extensively in human medicine for prophylactic and therapeutic treatment of unipolar and bipolar manic-depressive disorders.[10,11] Its use as a salt substitute for patients requiring low-sodium intake resulted in several unfortunate clinical episodes in the 1940s and led to its removal from the market.[12] Lithium's potentially toxic effects and pharmacokinetics have been documented in healthy and schizophrenic humans,[13,14] crossbred and Pietran pigs,[15] and Beagles and mixed-breed dogs.[16,17] We are not aware of any study of toxic effects and pharmacokinetics of lithium chloride in horses, and this information is needed as a prelude to wide acceptance of the method for use with client-owned horses. The purpose of the study reported here was to determine the pharmacokinetics of lithium chloride administered IV to conscious, healthy horses and to document any related systemic toxic effects.

Materials and Methods

Horses and health status—Six healthy adult Standardbred horses (3 females, 3 geldings) that weighed between 416 and 518 kg (mean ± SD, 471.2 ± 41 kg) were used in the study. All horses were used as teaching animals and were housed at our veterinary teaching hospital. Horses were accustomed to regular handling and acclimated to the environment, and they had not received drugs for ≥ 14 days before the study began. Experiments were begun early in the morning, and each horse was included in the study for a sin-

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gle day. Horses were given ad libitum access to water and a trace-mineral salt block, except when cross-tied during a 1-hour injection period. All horses were fed a diet of timothy grass hay; horses were fed twice daily in accordance with their normal schedule, which was 3 and 16 hours after injection of lithium chloride. The study was performed in accordance with the guidelines of the Canadian Council on Animal Care, and approval was granted by an institutional animal care committee.

The health status of each horse was determined on the basis of results of physical examination, evaluation of a 15-minute ECG tracing, and results of a CBC and serum biochemical analyses. A blood sample was obtained from each horse before the start of the study for use in determination of baseline lithium concentrations.

Instrumentation and protocol—The area over each jugular vein was infiltrated with a 2% solution of lidocaine hydrochloride, and a 14-gauge 14-cm catheter[c] was inserted percutaneously in each jugular vein. Blebs of lidocaine were inserted in the subcutis, and stainless-steel ECG electrodes were placed percutaneously in a base-apex configuration to permit continuous lead-II oscillographic ECG monitoring[d] and collection of a sample recording at specified sample intervals.

Sterile lithium chloride preparations (0.15 mmol/L) were prepared from an ultrafiltered stock solution (8 mmol/ml),[e] using aseptic dilution with sterile water. Final concentration was assessed by determining the chloride concentration at a reference laboratory. Dilutions were accurate to ± 3% (ie, 0.145 to 0.155 mmol/L). Aliquots (3 mmol) of lithium chloride were injected as a bolus injection (20-ml volume) in the right jugular vein at 3-minute intervals for 20 injections. Thus, the total dose of lithium chloride was 60 mmol/horse (0.13 ± 0.01 mmol/kg of body weight) administered during a 60-minute period

Collection of blood samples and clinical evaluation—All blood samples for analysis were collected from the left jugular vein. Blood samples for lithium analysis were collected into tubes containing EDTA immediately before the first injection (time 0) and 2.5, 5, 10, 15, 30, and 60 minutes and 4, 8, 12, and 24 hours after the last injection of lithium chloride. Serum was harvested immediately from the vials to prevent uptake of lithium by RBC. Analysis was performed by laboratory personnel, using flame photometry with internal standards assayed with each batch of serum samples. Limits of quantification were 0.01 to 10 mmol/L, and the coefficient of variation for the analytic method was < 2.1% during the period of analysis. Samples for hematologic and biochemical analysis were obtained 1 and 24 hours after injection of lithium chloride.

Auscultable **gastrointestinal tract (GIT)** motility was determined 1, 2, 4, and 24 hours after injection of lithium chloride, and 1-minute ECG tracings were recorded 15, 30, and 60 minutes after drug administration. The lead-II recording of the ECG was monitored continuously on the oscilloscope. Horses were monitored for changes in mentation and stance (excitability, apprehension, development of sedation, appearance of discomfort, ataxia) during the injection period, continuously for 1 hour after the last injection, and 4, 8, 12, and 24 hours after the last injection. At 15-minute intervals during the 1-hour postinjection period and at each sample collection period thereafter, each horse was forced to turn in tight circles in its stall and urged to walk to allow investigators to assess gait abnormalities or readily apparent muscle weakness. Gastrointestinal tract motility was assessed subjectively, using auscultation of 2 sites (30 s/site) in each of 4 abdominal quadrates (upper and lower, left and right). Normal borborygmus was defined as 2 to 3 sounds/min and assigned a score of 2, decreased was defined as 1 to 2 sounds/min and assigned a score of 1, and lack of borborygmus was assigned a score of 0. Thus, the maximum attainable score for each horse was 8. Assessment was made by 1 investigator (CLH) to minimize variability. Repeatability of the scoring method has been reported elsewhere.[18]

Pharmacokinetic analysis—Serum lithium concentrations were corrected for background values by subtracting any background concentration (before treatment) from the value for each sample obtained after treatment for that horse on that day. Pharmacokinetic analysis of the serum lithium decay curve after the 20th bolus dose was performed, using a computer software program.[f] Data were analyzed, using 2- and 3-component open models for bolus IV injection, and selection of the appropriate model depended on Akaike information criterion[19] as calculated on the residuals following iterative curve fitting of the data for each specific horse as well as mean values for all horses. Growth curves that estimated the change in lithium concentrations resulting from 20 successive bolus injections of lithium were obtained for 3- and 6-minute injection intervals by back-fitting to the lithium concentrations of the first injection, based on decay variables, and adjusting this value to 1. This fit closely the growth component ($r = 0.9999$) to the following second-degree polynomial equation:

$$y = a_0 + a_1x + a_2x^2$$

where y is the predicted relative change in serum lithium concentration, a_0 is a constant function with $y > 0$, a_1 is the growth function relative to x, a_2x^2 is a special quadratic function where $a_2 < 0$, and x is time (0 to 150 minutes for the 3-minute intervals and 0 to 200 minutes for the 6-minute intervals).

Statistical analysis—A 1-way ANOVA for repeated measures was used to compare hematologic and biochemical values for samples obtained 1 and 24 hours after the last injection with values for samples obtained before injection, using a 95% confidence interval. The ECG strips obtained before and after injection were analyzed to determine height of the T wave, evidence of blockade of the sinoatrial node, widening of QRS complexes, length of the ST segment, and evidence of any cardiac dysrhythmias. Values before and after injection were compared, using a paired *t*-test with a 95% confidence interval. Nonparametric GIT motility scores were compared, using the Wilcoxon 2-sample test for values obtained before and after injection.

Results

Pharmacokinetic model—Lithium chloride concentrations in 5 of 6 horses and the mean data best fit a 3-compartment open model after bolus injection. Data for the other horse best fit a 2-compartment model for bolus administration; that horse was missing data for the sample collected at 0.5 hours and had the lowest corrected concentrations of serum lithium. The following equation described the mean lithium decay variables after 20 bolus injections:

$$C = 0.1719e^{-3.2742 \cdot t} + 0.2801e^{-0.3688 \cdot t} + 0.1089e^{-0.0167 \cdot t}$$

where c is concentration, e is the base of natural log, and t is time. Individual and group mean Y intercept, rate of elimination, harmonic mean half-life, and transfer microconstants for horses were calculated (**Table 1**). Terminal half-life ranged from 32 to 84 hours (mean, 43.5 hours), as determined on the basis of data for the 5 horses in the 3-compartment model,

Table 1—Serum lithium decay variables in 6 horses following twenty 3- mmol doses of lithium chloride administered as bolus IV injections at 3-minute intervals

Variable	Horse 1	2	3	4	5	6	Mean for all	Mean (range) for 5 horses*
C_{0s} (mmol/L)	0.5294	0.6132	0.5702	0.5495	0.4914	0.542	0.5465	0.5608 (05294–0.6132)
A (mmol/L)	0.1163	0.2235	0.2317	0.1334	0.3514	0.1544	0.0926	0.1719 (0.1163–0.2317)
B (mmol/L)	0.3283	0.2937	0.1914	0.3009	0.14	0.2864	0.3283	0.2801 (0.1914–0.3283)
C (mmol/L)	0.085	0.096	0.1471	0.1152	ND	0.1012	0.1256	0.1089 (0.085–0.1471)
α (/h)	5.216	2.4174	1.3062	5.1539	0.6894	2.2774	2.9857	3.2742 (1.3062–5.2160)
β (/h)	0.3707	0.3447	0.3818	0.4093	0	0.3374	0.5155	0.3688 (0.3374–0.4093)
γ (/h)	0.021	0.013	0.01	0.02	ND	0.017	0.0151	0.0162 (0.010–0.0210)
$t_{1/2\alpha}$ (h)	0.1329	0.2867	0.5307	0.1344	1.005	0.304	0.2322	0.2116 (0.1329–1.005)†
$t_{1/2\beta}$ (h)	1.87	2.011	1.8155	1.6934	331.6	2.054	1.3447	1.8795 (1.693–2.054)†
$t_{1/2\gamma}$ (h)	31.736	53.562	84.049	34.547	ND	41.7	45.994	43.473 (31.736–84.049)†
K10 (/h)	0.1104	0.073	0.031	0.085	0.01	0.077	0.0607	0.0753 (0.031–0.1104)
K12 (/h)	0.9992	0.6466	0.2865	1.0841	0.4863	0.4825	0.3696	0.6998 (0.2865–1.0841)
K21 (/h)	4.1371	1.6371	0.8842	3.9777	0.1979	1.7044	2.547	2.468 (0.8842–4.1371)
K13 (/h)	0.2691	0.3281	0.3437	0.311	ND	0.2703	0.3889	0.3044 (0.2703–0.3437)
K31 (/h)	0.092	0.09	0.1511	0.1259	ND	0.097	0.15	0.1112 (0.090–0.1511)

*Arithmetic mean value for the 5 horses in which the serum concentration vs time data best fit a 3-compartment open model for IV bolus injection; data for horse No. 5 best fit a 2-compartment open model. †Harmonic mean for the data of the 5 horses that best fit the 3-compartment model.

C_{0s} = Adjusted (baseline zero) mean peak serum concentration, determined as A + B + C. A, B, and C represent the Y-intercept for the α, β, and γ decay curves, respectively. Thus, α and β are the rates of decay from the first and second compartments, respectively, and γ is the rate of decay for the first, second, and third compartments at equilibrium. The half-life values for the first, second, and third compartments are $t_{1/2\alpha}$, $t_{1/2\beta}$, and $t_{1/2\gamma}$, respectively. K10, K12, K21, K13, and K31 = Microconstants describing the rate of movement of lithium among the 3 compartments of the model. ND = Not determined.

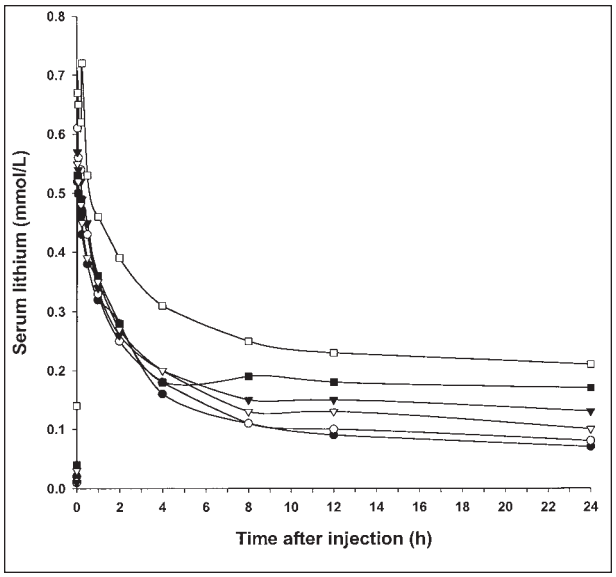

Figure 1—Serum lithium concentrations detected in 6 horses following twenty 3.0-mmol doses of lithium chloride (0.15 mmol/L) given IV as bolus injections at 3-minute intervals. Each symbol represents values for 1 horse. Time 0 is immediately before the first injection; subsequent times are after the last injection.

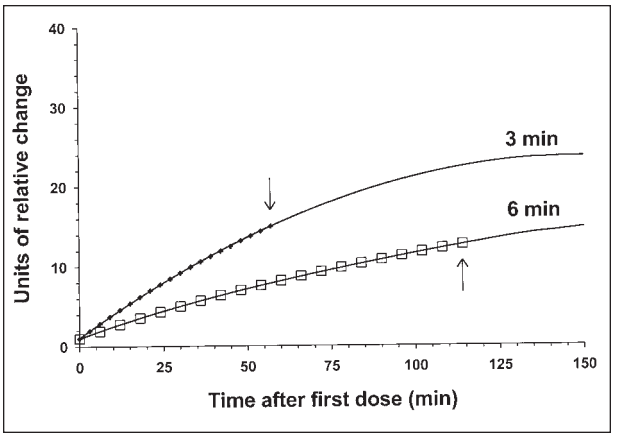

Figure 2—Estimated growth curves of serum lithium concentrations for repeated bolus injections of 3.0 mmol of lithium chloride administered at 3- or 6-minute intervals, as determined on the basis of experimentally determined decay variables. Theoretic concentration for time 0 (after the first dose) has been adjusted to a value of 1. The last (20th) injection for each interval is indicated (arrow).

and **adjusted (baseline zero) mean peak serum concentration (C_{0s})** was 0.5608 mmol/L after 20 injections. Actual peak serum concentration measured at 2.5 minutes ranged from 0.52 to 0.67 mmol/L (mean ± SD, 0.575 ± 0.056 mmol/L). Serum lithium concentrations before treatment ranged from 0.01 mmol/L for 2 horses to 0.04 mmol/L for 1 horse, which was the horse that best fit the 2-compartment model. Maximum estimated C_{0s} for that horse was 0.6132 mmol/L. After 24 hours, lithium concentration ranged from 0.07 to 0.21 mmol/L (mean, 0.13 ± 0.05 mmol/L; **Fig 1**). Maximum serum lithium concentrations were observed at 2.5 minutes in all horses, except 1 horse that had a peak serum value 15 minutes after injection.

Estimates of the relative accumulation of lithium following repeated injections were calculated, using mean serum data (**Fig 2**). These were based on data from the decay variables determined after 20 injections given at 3-minute intervals. Growth in the adjusted lithium concentrations fit the increasing phase of a second-degree polynomial function (r = 0.9999) for the period of 0 to 150 minutes. Although the data obviously did not fit a full second-order polynomial function outside the time boundaries described, the value for r was higher than for a simple exponential growth function achieving an asymptote. When administered at 3-minute intervals, 20 injections would produce concentrations of lithium that would increase to approximately 15 times that

Table 2—Mean ± SD values for hematologic variables after IV injection of 60 mmol of lithium chloride in 6 horses

Variable	Before injection	After injection	
		1 h	24 h
WBC ($\times 10^9$ cells/L)	5.62 ± 0.82	5.48 ± 0.75	5.92 ± 0.58
RBC ($\times 10^9$ cells/L)	7.87 ± 0.70	7.11 ± 0.39	7.47 ± 0.55
Hemoglobin (g/L)	127.33 ± 14.69	115.00 ± 7.77	120.33 ± 10.82
Hematocrit (%)	0.33 ± 0.04	0.30 ± 0.02	0.32 ± 0.03
Platelets ($\times 10^9$ cells/L)	132.60 ± 23.28	124.80 ± 25.78	131.50 ± 51.11
Neutrophils ($\times 10^9$ cells/L)	2.68 ± 0.29	3.05 ± 0.63	3.24 ± 0.76
Lymphocytes ($\times 10^9$ cells/L)	2.76 ± 0.99	2.24 ± 1.25	2.50 ± 1.16
Monocytes (10^9 cells/L)	0.09 ± 0.05	0.15 ± 0.07	0.06 ± 0.01

Values did not differ significantly ($P < 0.05$) among the 3 time periods for any variable.

Table 3—Mean ± SEM values for biochemical variables after IV injection of 60 mmol of lithium chloride in 6 horses

Variable	Before injection	After injection	
		1 h	24 h
Calcium (mmol/L)	2.82 ± 0.11	2.85 ± 0.08	2.90 ± 0.12
Phosphorus (mmol/L)	1.14 ± 0.17	1.19 ± 0.15	1.11 ± 0.16
Sodium (mmol/L)	137.17 ± 1.17	137.00 ± 2.21	136.83 ± 1.83
Potassium (mmol/L)	4.12 ± 0.38	3.85 ± 0.27	4.23 ± 0.27
Chloride (mmol/L)	93.67 ± 3.83	94.17 ± 3.31	93.33 ± 2.73
Total protein (g/L)	62.17 ± 2.31	61.33 ± 1.97	61.33 ± 2.66
Albumin (g/L)	32.83 ± 1.94	32.00 ± 2.61	31.83 ± 1.72
Globulin (g/L)	29.33 ± 1.51	29.33 ± 1.21	29.50 ± 1.05
Urea (mmol/L)	4.40 ± 0.25	4.38 ± 0.25	4.05 ± 0.24
Creatinine (umol/L)	126.33 ± 18.66	126.50 ± 18.61	120.33 ± 15.74
Glucose (mmol/L)	4.52 ± 0.38	5.05 ± 0.45	4.60 ± 0.62
ALP (U/L)	106.67 ± 17.93	102.50 ± 17.94	101.50 ± 17.32
GGT (U/L)	11.83 ± 3.0	13.17 ± 4.6	11.33 ± 3.33
AST (U/L)	312.67 ± 50.78	307.17 ± 53.36	304.67 ± 44.08
CK (U/L)	146.33 ± 25.36	139.67 ± 27.78	150.00 ± 32.36
GMD (U/L)	1.67 ± 0.82	1.83 ± 0.75	1.50 ± 0.55
Haptoglobin (g/L)	0.90 ± 0.27	0.83 ± 0.17	0.90 ± 0.14
Total bilirubin (mmol/L)	31.00 ± 10.95	33.17 ± 10.74	30.00 ± 11.56
Conjugated bilirubin (mmol/L)	2.17 ± 0.41	2.00 ± 0.00	2.00 ± 0.00

Values did not differ significantly ($P < 0.05$) among the 3 time periods for any variable.

ALP = Alkaline phosphatase. AST = Aspartate transaminase. GGT = γ-Glutamyltransferase. CK = Creatine kinase. GMD = Glutamate dehydrogenase.

achieved after the first injection and a plateau in approximately 150 minutes if bolus injections were continued at the same rate. The same decay variables were used to estimate the extent of accumulation of lithium in the serum if the doses had been administered at 6-minute intervals instead of 3-minute intervals. Concentrations would be expected to increase to 12 to 13 times the initial concentrations by the 20th injection, and a plateau would be achieved at approximately 200 minutes after the first injection if injections were continued at the same rate. Plateau concentrations estimated from the graph of values for the extrapolated 3-minute intervals would be > 30 times the concentration after the first injection and about twice the C_{0s} of 0.5465 mmol/L achieved after the 20th injection. Plateau concentrations estimated for a 6-minute treatment interval would be approximately 15 times greater than the concentrations after a single dose, equivalent to a C_{0s} in the range of 0.5 to 0.6 mmol/L.

Toxic effects—Signs of toxic effects were not observed. Mentation, stance, or behavior did not change during any portion of the study; however, there was an apparent increase in urine output during the first 8 hours in 3 horses. The Wilcoxon 2-sample test for GIT motility did not reveal significant differences between mean baseline score (5.5 ± 1.52) and mean scores determined 1 (4.7 ± 1.37), 2 (5.0 ± 0.89), 4 (7.8 ± 0.41), and 24 (5.5 ± 1.38) hours after treatment. There was not a significant difference in height of the T wave, frequency of blockade of the sinoatrial node, QRS width, or length of the ST segment between values before and after injection. Cardiac arrhythmias were not detected at any point, except for normally occurring second-degree atrioventricular-node block. Hematologic and biochemical values 1 and 24 hours after injection did not differ significantly in response to lithium administration. Hematologic and biochemical variables had good agreement between values obtained before injection and 1 and 24 hours after injection (**Tables 2 and 3**).

Discussion

Pharmacokinetic variables may vary widely among species. Similar to sodium, lithium is filtered via the glomerulus and is reabsorbed by the proximal but not the distal renal tubules in humans.[20] It is distributed throughout total body water and excreted almost entirely by the kidneys. The half-life of lithium is 11.2 to 21.6 hours in dogs,[16,17] 11.2 to 18.6 hours in pigs,[15] and 19.8 to 41.3 hours in humans.[13,14] In the study reported here, calculated mean terminal half-life of lithium in horses was 43.5 hours following 20 successive 3.0-mmol bolus injections given at 3-minute intervals. Variability in total body clearance and half-life of lithium has been reported between purebred and mixed-breed animals.[17,21] It is unknown if this variability had an impact on our data, because all horses in our study were of the same breed (ie, Standardbred).

The decision to perform a study of toxic effects by administering a series of discrete boluses, compared with administering 1 large bolus or a continuous infusion, was made on the basis that the experimental conditions would be similar to the anticipated method for use of lithium chloride as an indicator in dilution studies.[1,5] Mean cumulative dose of lithium chloride in horses in our study was 0.13 ± 0.01 mmol/kg (expressed on a body-weight basis). Lithium disposition is normally addressed, at least in humans, in terms of steady-state kinetics because of the long-term nature of the therapeutic exposure. However, for measurement of cardiac output in horses by use of multiple frequent administrations, serum concentrations of the drug are influenced by all 3 decay rates. Others have used a 2-compartment model to describe the pharmacokinetics of single-dose IV administration of lithium in dogs.[17,21] The fact that the data for our study best fit a 3-compartment model may have been attributable to repeated lithium administration.

On the basis of observations in the study reported here, it appears that healthy horses are virtually unaffected by cumulative doses of lithium chloride that are at least twice the total dose anticipated for a series of injections that would be used in measurement of car-

diac output. A dose of 2.25 mmol provided an adequate signal for a single cardiac output determination in anesthetized horses weighing 480 to 620 kg.[5] Because the accuracy of the lithium detector is influenced by the accumulation of background plasma lithium concentrations, and an upper limit for background concentrations of 0.2 mmol/L has been recommended,[g] the maximum number of replicated determinations during a reasonable period of drug (ie, treatment) administration (2 to 4 hours) is estimated to be ≤ 10 (eg, total dose of lithium chloride, 22.5 mmol).

Concentrations detected after 20 injections were much lower than those that reportedly cause toxic effects in other species. In humans, mild toxic effects including discomfort, ataxia, thirst, nausea, vomiting, abdominal pain, and diarrhea begin to appear when steady-state serum concentrations reach 1.6 mmol/L.[22,23] Confusion, convulsions, spasticity, dehydration, and coma may develop at a concentration of 3.0 mmol/L, and 3.5 mmol/L is considered to be the lethal plasma concentration in humans.[10] In dogs, moderate toxic effects are observed at a concentration of 1.5 mmol/L and are characterized by polyuria-polydipsia, general weakness, dehydration, and diarrhea.[21,24] Seven-week-old pigs had signs of lethargy, tremors, vomiting, decreased appetite, ocular discharge, and circulatory abnormalities at serum concentrations of 1.25 to 10.78 mmol/L.[25] In our study, peak serum lithium concentrations (ie, C_{0s}) ranged from 0.4914 to 0.6132 mmol/L (mean, 0.5493 mmol/L), indicating that even during acute administration, lithium chloride injections as frequent as every 3 minutes produced concentrations well below those documented to cause toxic effects in other species. It is worth mentioning that all herbivores have trace amounts of lithium as a consequence of their forage or grass diets, and some amount of lithium intake seems essential for goats.[26] Indeed, baseline serum concentrations of lithium were between 0.01 and 0.04 mmol/L in the horses reported here.

Background concentrations observed in our study were not sufficiently high to interfere with performance of a lithium-dilution cardiac output study.[5] If the monitoring of cardiac output were to be maintained beyond 20 injections, the projected concentration of lithium in plasma would still be much less than toxic amounts (Fig 2). A longer interval between injection of successive bolus doses is most likely when the technique is actually used and would further reduce the peak lithium concentrations, as illustrated for a 6-minute interval.

Terminal half-life variables that ranged from approximately 32 to 84 hours would suggest that during a cardiac output monitoring procedure that required 1 hour, < 3% of the dose of lithium would be eliminated, even in horses with the shortest half-life. Renal elimination and terminal half-life would not play a large role in determining plasma concentrations of lithium in typical cardiac output monitoring. Distributive pharmacokinetic variables α and β would play a more important role. Thus, factors such as dehydration would be expected to have a major impact on plasma lithium concentrations in this context, whereas altered renal function would influence the plasma concentration much less.

The increased urination observed in 2 of 6 horses in this study may have been similar to that in humans in which impaired renal concentrating ability attributable to the inhibitory effect of lithium on intracellular adenosine monophosphate formation in the renal tubules has been documented.[20] Caution should be exercised when using lithium chloride in animals that are known to be dehydrated or that have impaired renal function. Although a number of interactions between lithium and other drugs have been described,[27] those are all associated with chronic administration of lithium, and none of the possible interactions would appear to have any relevance to acute use of lithium chloride for determination of cardiac output. The long half-life of 43.5 hours means that there would be virtually no clearance of lithium during most acute studies of cardiac output. Investigators would have to exercise care when using this method for measurement of cardiac output because of the increasing background concentrations with successive measurements (Fig 2). This increased background concentration could ultimately interfere with subsequent lithium measurements, because the lithium-sensitive electrode progressively loses sensitivity as plasma lithium concentrations increase. The manufacturer recommends a maximum background plasma concentration of 0.2 mmol, which is well below the nontoxic serum concentrations observed in the horses of this study.

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