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Is lithium a candidate to modify rutting behaviour in stags?

M.F. PROUTING, A.M. NICOL AND M.J. KEELEY

Animal and Food Sciences Division, PO Box 84, Lincoln University, Canterbury

ABSTRACT

Preliminary experiments assessed the potential of lithium to moderate the effects of the rut. Young (5-9 month old) stags were used to determine the kinetics of lithium in deer, establish appropriate dose rates, evaluate the opportunity for self-medication and to test whether behaviour would be modified.

The relationship between lithium dose rate and plasma lithium concentration was established from acute administration (5 dose rates, 2 animals per dose) and confirmed with continuous medication for 31 days. A daily dose of 0.6 mmol Li/kg W (as LiCl) achieved a mean plasma Li concentration of (0.78 ±0.04 mmol/l), which was within the therapeutic range (0.5-1.5 mmol/l).

This daily dose, offered in drinking water (11.2 mmol Li/l as LiCl) to a group of (n=10) young stags induced a decline in both water (14%) and feed (12%) intake which was almost recovered after 4 weeks of self-medication. Liveweight gain averaged 252 ±27 g/d for +Li animals compared with 263 ±21 g/d for the -Li group (NS).

Lithium treated stags moved more freely through a maze than did -Li stags, with 60% of the animals completing the maze compared with only 10% of the -Li group. There was no significant difference in the behaviour of +Li and -Li groups to the introduction of a unfamiliar stag or in their response to human handling. This work lays the foundation for studies on the potential for lithium therapy to modify the rut in adult stags.

Keywords: deer, rut, lithium, behaviour

INTRODUCTION

Entire male deer are farmed in New Zealand for the annual harvest of their velvet antler. Stags display aggressive behaviour during the breeding season (autumn) that poses a potential threat to their welfare, to the welfare of their handlers and to the environment (Nicol & Keeley, 2002).

Currently farmers mitigate behavioural problems associated with bachelor groups of adult stags by increasing the grazing area, effectively reducing the stocking density (Moore *et al.*, 1985). Stags not displaying agonistic behaviours typical of the rut would be safer to handle and could be grazed together within smaller areas, allowing autumn pasture to be saved for winter, possibly alleviating winter feed costs and management difficulties.

Cryptorchidism (Nicol & Keeley, 2002) and immunocastration (Freudenburger *et al.*, 1993; Barrell *et al.*, 2002) are techniques that have been explored to modify stag behaviour during the rut, however neither has proved commercially acceptable.

Use of behaviour-modifying medication is another potential option, as treatment could be applied temporarily during the breeding season (March, April and May), providing it did not disrupt the velvet antler cycle. The use of long-acting neuroleptics has been shown to lessen the response of deer to handling stressors (Diverio *et al.*, 1993) but their prolonged use over the rut is impractical. Lithium is a mood-modifying drug used safely in human bi-polar patients to prevent mood swings (Pilcher, 2003) and has reduced

aggressive behaviour in pigs (McGlone *et al.*, 1981) and calmed bulls (O'Kelly & Spiers, 1994). This study is a preliminary investigation into the potential use of lithium in this role.

MATERIAL AND METHODS

Two experiments were carried out during June-September 2003 with 5-9 month old red deer (*Cervus elaphus*) stags (mean liveweight 53.9 ±4.66 kg). Stags were housed indoors in pens (n=10, Experiment 1) or in groups (n=2 groups of 10, Experiment 2) and offered a diet of nuts (All Purpose Ration, Weston Animal Nutrition, Rangiora, 849g DM/kg fresh weight, 823g DOM/kg DM, 160g crude protein/kg DM, 10g fibre/kg DM, 2.5g fat/kg DM, and ME content = 12.7 MJ ME/kg DM) *ad libitum*.

For experiment 1, stags were assigned by liveweight to one of 5 acute oral dose rates, 0, 0.25, 0.5, 0.75, and 1.0 mmol LiCl/kg liveweight (which corresponded to 0, 1.08, 3.47, 5.21, and 6.94 mg Li/kg liveweight (W) respectively) with two animals per dose rate. Each dose of LiCl was administered in 200 ml water *per os* and sequential blood samples taken by jugular venepuncture at 0, 2, 6, 12, 18, 24, 48, 72, 96, 120, 144 and 168 h following dosing. When plasma lithium levels had returned to base level, stags were re-allocated to the dose rates and the procedures repeated. Plasma was separated by centrifugation within 4 h of sample acquisition and stored at -20°C for further analysis. Plasma lithium concentration was determined by flame emission spectrophotometry at 670.7 nm using

a Perkin-Elmer 5100 PC (USA) atomic absorption spectrophotometer in emission mode. A dose response relationship was established from these data.

Experiment 2 involved the chronic administration (31 days) of 0 (-Li group) and 0.6 mmol (+Li group) LiCl/kg W/d to groups of young stags. Lithium chloride was dissolved in drinking water (3.5-4.0 l/stag/day) at a concentration of 9.9 to 11.6 mmol LiCl/l. Previously it had been established that young deer accepted a similar daily dose in drinking water. The -Li group were offered unmedicated water. Lucerne chaff (878g DM/kg fresh weight, 600g DOM/kg DM, 18g crude protein/kg DM, 32g fibre/kg DM and ME content = 9.7 MJ ME/kg DM) was offered *ad libitum* in addition to nuts *ad libitum*. Blood samples were taken 7, 10, 14, 21 and 28 d after the start of treatment and processed as in Experiment 1. Group food (alternate days) and water (daily) intake were recorded. The stags were weighed weekly without prior fast. Right pedicle length of all stags was recorded on August 29 and September 12.

The effect of lithium therapy on aspects of behaviour was assessed in three ways. An unfamiliar stag was introduced to both +Li and -Li groups and aggressive behaviours directed at the intruder recorded. The response to human restraint in terms of 'time to stillness' when held was recorded for each animal. A 'maze' sequence of 7 deer-yard doors were left ajar and each animal was individually removed from its cohort and released into the first pen of the sequence. The final pen in the maze was adjacent to the stags' pen-mates. The stag's location in the pen sequence was recorded 150 seconds after release.

Treatment effects on feed and water intake, expressed $/W^{0.75}/d$ were analysed by an analysis of variance with treatment group and week as fixed effects.

Liveweight gain was calculated for each animal by fitting a linear regression of liveweight against time. Mean liveweight gain of +Li and -Li groups was compared using an analysis of covariance with initial live weight as the covariate. A 2-sample t-test was used to compare pedicle length and frequency data from the maze was subjected to a χ^2 test.

The experimental protocol was approved by the Lincoln University Ethics for Experimentation on Animals Committee.

RESULTS

No signs of lithium toxicity (e.g. tremor, thirst, lethargy, vomiting) were apparent in any animal following any of the lithium treatments (acute or chronic) with the exception of one animal that displayed polydipsia for two days following an acute dose of 0.5 mmol LiCl/kg during the second week of Experiment 1.

The linear regression of the natural log (ln) of sequential plasma concentrations against time were fitted

for each dose and each animal. Highly significant ln-linear regressions were obtained for all animals (mean $R^2 = 0.983$). The rate constant (k) was relatively constant at 0.031 ± 0.001 regardless of dose rate (Table 1). Lithium concentration at time zero (T_0) was predicted from the regression equations and was directly proportional to dose rate (Equation 1); an increase in dose of 1.0 mmol/kg W induced close to a 1.0 mmol/l increase in T_0 plasma lithium concentration. The intercept value was close to zero.

$$Y = 0.949 \pm 0.054 X - 0.03 \pm 0.03, R^2 = 0.957, P < 0.001. \text{(Eq 1)}$$

where Y = T_0 plasma lithium concentration (mmol/l) and X = lithium dose rate (mmol LiCl/kg W).

TABLE 1: The mean and standard deviation (SD) of the time zero (T_0) plasma lithium concentration, rate constant (k) and half life ($T_{1/2}$) of 4 acute dose rates of lithium chloride given in aqueous solution to young red

		Dose rate (mmol LiCl/kg W)			
		0.25	0.5	0.75	1.0
T_0 (mmol/l)	mean	0.225	0.444	0.632	0.954
	SD	0.013	0.033	0.049	0.088
k (/h)	mean	-0.034	-0.034	-0.028	-0.029
	SD	0.004	0.003	0.004	0.006
$T_{1/2}$ (h)	mean	20.5	20.5	25.5	24.3
	SD	2.71	1.72	3.79	4.46

deer stags. (4 observations per mean).

These data were used to calculate the flow rate from the lithium pool and thus estimate the daily dose required to maintain a specific plasma Li concentration under continuous administration. On this basis, a daily dose of 0.6 mmol LiCl/kg W, was chosen to achieve stable plasma lithium concentration of 0.78 mmol/l (midway in the range of therapeutic concentrations in humans) in the chronic experiment (Experiment 2). Figure 1 shows the mean plasma concentration of +Li and -Li stag groups self-medicating on a dose of 0.6 mmol Li+/kg W/d during a 28-day period. Plasma concentration of +Li treated animals was maintained at around 0.8 mmol/l from day 7.

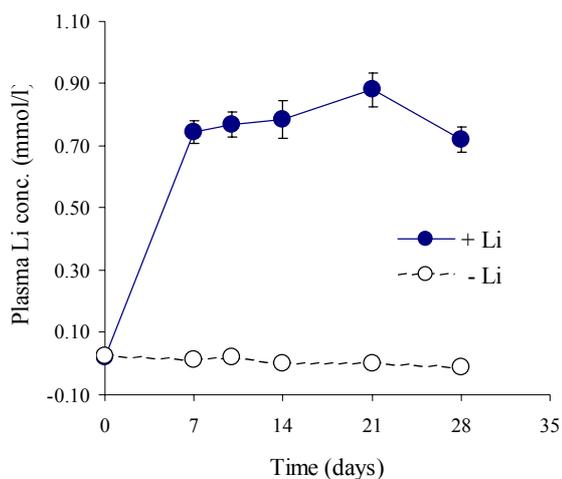
Mean voluntary food intake (VFI) and water intake were significantly lower for the self-medicating +Li stags than for the group of controls (-Li), by 14% in both cases, $P < 0.05$ (Table 2). These differences were greater in the first two weeks of treatment than in the later two weeks. There were no significant differences between groups in the rate of liveweight gain (LWG) or on rate of pedicle extension.

TABLE 2: Mean voluntary feed intake, water intake, live weight gain (LWG) and increase in pedicle length of groups (n = 10) of young red deer stags chronically self-medicated with lithium chloride in their drinking water (+Li) or offered unmedicated water (-Li).

Treatment group	Voluntary food intake (gDM/kg W ^{0.75} /d)	Voluntary food intake (gDOM/kgW ^{0.75} /d)	Water intake (ml/kg W/d)	LWG (g/d)	Pedicle length (increase cm)
- Li	73.9a	58.0a	63.5a	263a	1.9a
+Li	65.2b	49.9b	54.4b	252a	1.8a
sem	3.16	2.34	2.02	24	0.53

Within columns, means followed by a different letter are significantly different (P<0.05)

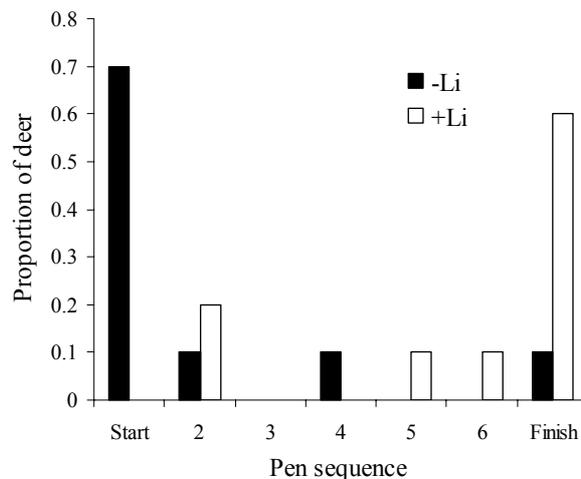
FIGURE 1: The time course of the mean plasma lithium concentration of groups (n = 10) of young red deer stags chronically self-medicated with lithium chloride in their drinking water (+Li) or offered unmedicated water (-Li) for 28 days (vertical bars represent the standard error of the mean).



Control and chronic lithium treated young stag groups selected differing proportions of chaff and nuts. Lucerne chaff intake by the +Li group increased from 0.21 to 0.40 of total VFI_{DM} (P<0.05) during the treatment period. This was in contrast to -Li stags where the proportion of chaff in the diet remained between 0.18 and 0.21 of total VFI_{DM}.

The mean incidences of the aggressive behaviours directed at an unfamiliar animal was not significantly different nor was there any significant difference in reaction time to the human restraint between the +Li and -Li groups of stags. The distribution of +Li treated stags through the sequence of pens in the maze (Figure 2) was very different to that of -Li stags (P<0.001). A high proportion (0.70) of -Li stags had not progressed from the start pen. In contrast 0.60 of +Li animals had found their way to the end of the maze.

FIGURE 2: The proportional distribution of groups (n = 10) of young red deer stags chronically self-medicated with lithium chloride in their drinking water (+Li) or offered unmedicated water (-Li) for 28 days, 150 sec after their release from the starting pen in a 7 pen maze.



DISCUSSION

On the basis of this work, lithium should be considered a candidate for the suppression of agonistic behaviour in *adult* stags during the breeding season. The pharmacokinetics of the drug in the young stags used in this study and the evidence for self-medication via drinking water, suggest the maintenance of constant plasma lithium levels can be readily achieved. A definite behaviour change was detected in young deer after chronic lithium therapy suggesting potential for an effect in adult rutting stags where the levels of aggression are higher.

Suppressed voluntary feed intake with chronic lithium administration in deer is consistent with the consequences of its chronic use in bulls (O'Kelly & Spiers, 1994) but in contrast to those in pigs where

serum lithium concentrations as high as 0.7 mmol/l had no effect on daily feed intake (McGlone *et al.*, 1981). Suppression of VFI by lithium might not be a feature of the drug use in adult stags during the breeding season. VFI in stags during the rut is already severely restricted due to seasonal inappetence (Drew 1993, Freudenberger *et al.*, 1993; Barrell *et al.*, 2002) so the effect of lithium on VFI might be negligible in this circumstance. This would be consistent with the effect of lithium (0.5 mmol LiCl/kg/d) in bulls where feed intake was reduced in bulls fed *ad libitum* but not when offered a restricted diet (about 50% *ad libitum*) (O'Kelly & Spiers, 1994).

The short-term reduction in water intake with lithium therapy may be attributable to the salty taste of lithium or to induced changes in rumen osmolarity (O'Kelly & Spiers, 1994). Ternouth & Beattie (1971) reported that salt solutions added to the rumen liquor of sheep before a meal led to a decrease in food intake. The precise reason for the change in diet preference with lithium medication is not apparent. A lack of sodium in the diet can exacerbate lithium toxicity (Rang *et al.*, 1999) but, on the other hand, sodium retention can be a side effect of lithium treatment (Rang *et al.*, 1999). Any such disruption to cation homeostasis might influence diet selection for sodium. There was no opportunity to measure the sodium content of either the chaff or the nuts to test this hypothesis.

The significant reduction in VFI was not reflected in significantly lower live weight gain. Considerable work on the composition of live weight gain or changes in metabolic rate under lithium therapy (Rang, *et al.*, 1999) would be needed to explain this apparent paradox. This minimal change in live weight would be favourable in the context of adult rutting stags on lithium.

Significant modification to behaviour by lithium was discovered during the maze experiment. The difference may represent a calming effect, similar to that reported by Diverio *et al.*, (1993) with the use of long-acting neuroleptics, where treated animals exhibited more normal behaviour patterns than control animals. The implications of a calming influence of lithium are that stags during the rut would be more tolerant of their environment and of each other; could be grazed together within smaller areas (allowing for less feed wastage with the potential saving of autumn pasture); and be handled more safely. Alternatively the relatively greater daring of the lithium treated stags could be interpreted as reduced inhibition. If this were the case, lithium may have the potential to exacerbate aggressive behaviour in mature stags during the breeding season. However, there was no evidence for increased aggression in the young stags in this study.

The plasma lithium concentration achieved by chronic self-medication in deer in this study was higher than those that influenced behaviour in bulls and pigs but not as high as the most efficacious concentration in humans. There could be scope for increasing the plasma Li concentration in deer, but in humans the therapeutic index for this drug is quite narrow (BNF, 1996).

On commercial deer farms without trough-based stock water systems, alternative methods of medication

would be needed. Lithium, incorporated into feed at therapeutically relevant concentrations, has been accepted by pigs (McGlone *et al.*, 1981) and sheep (Mormede & Ledoux, 1980). There may be potential for administering lithium by dusting or spraying pasture, similar to that used in the application of calcined magnesite to dairy pastures. The administration of lithium chloride as an oral slow-release bolus is not feasible due to the large mass of daily lithium required.

The potential use of lithium, which is plentiful and inexpensive (O'Kelly & Spiers 1994), to modify behaviour in mature stags during the breeding season should be considered on the basis of this study. A chronic daily dose of lithium chloride can achieve stable and predictable plasma lithium concentrations in deer. Self-medication, through administration of lithium chloride in drinking water was successful. A further study into the use of lithium in adult stags to modify behaviour and liveweight change during the rut is suggested.

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