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Combined Effects of Alcohol and Lithium on Body Composition in the Rat Model

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WANG, J., J. POLLACK, D. BIRNKRANDT, L. DEMIRIAN, I. GRATTON AND R. N. PIERSON, JR. *Combined effects of alcohol and lithium on body composition in the rat model.* PHARMAC. BIOCHEM. BEHAV. 14(1) 41–47, 1981.—Alcohol markedly enhances Li^+ retention in blood and muscle in rats taking $Li^>$ and alcohol. The marked enlargement of the exchangeable Na^- space which occurs with alcohol alone, Li^+ alone, and to an even greater extent with combined therapy, results from extensive mobilization of "bound" bone sodium, which is transferred to intracellular sites, demonstrably in skeletal muscle, and presumably in other cells. This 87% increase in measured intracellular Na^+, and concomitant decrease in K^+, would be predicted to produce profound effects on the intracellular ionic milieu, and on membrane function. Lithium is associated with a decrease in food and fluid intake, and this effect is enhanced by alcohol. However the decrease in intake did not result in nutritionally significant deficits in either group, and therefore the observed abnormalities in body composition did not result from caloric, protein, K, Na, or Ca deficiency.

Lithium Alcohol Bone sodium Intracellular sodium Extracellular water

BOTH alcoholism [9, 16, 21] and manic-depressive disease [5, 16, 23] have been associated with intracellular sodium retention and potassium depletion. Lithium therapy has also been associated with effects on Na^+, K^+, and water distribution in many physiological circumstances, including affective disorders [2, 4, 10], and in normal animal models [2,7]. Currently fashionable treatment protocols propose lithium in alcoholism [19, 22, 27], often in settings where prior characterization of electrolyte status is not possible, and on a scale which escapes the possibility of close control of individual cases via frequent monitoring of lithium and electrolytes. Therefore detailed evaluation of the interactions of lithium and alcohol on electrolytes is needed, perhaps urgently, to lay a firmer groundwork for understanding predictable complications of this therapy.

METHOD

One hundred and eight mature Sprague-Dawley rats (320 ± 18 g, ten weeks of age) were randomly separated into alcohol (24), lithium (24), alcohol plus lithium (24), and control groups (36). In each group rats were housed no more than four per cage in a temperature controlled environment. The cages were 490 cubic inches for individual rats, and 1224 cubic inches for up to four rats, as required by NIH guidelines for rats of this size. Alcohol rats were fed rat chow ad lib, with 20% ethanol in H_2O as the only water source. Li^+-alcohol rats were given 30 mM of LiCl solution in 20% ethanol, the dose being selected to provide 10 mg/kg/day, an equivalent of the human therapeutic dosage [12]. Lithium rats were fed with 10 mM LiCl solution in tap water, which was one third of the Li^+ concentration given to the Li^+-alc group. This dosage was based on a previous study which showed that alcoholic rats consumed only one-third of the water taken by control rats [26]. In fact, the Li^+ dosed rats took much less LiCl solution than had been predicted, and the absorbed Li^+ doses were not comparable in the two groups of rats. Tap water was given to the controls.

Purina rat chow was provided all rats ad lib. Total intakes of chow and fluid were measured three times a week, and rat weights recorded weekly. Food and fluid comsumption were measured per cage, and divided by the number of rats per cage. The data presented in this report are the means and one standard deviation for the averaged data from each cage.

Total body water (TBW), extracellular water (ECW), and exchangeable sodium (Na_e) were measured in eight rats from each study cohort at 2, 5, and 9 weeks. The number of controls studied at 0, 2, 5, and 9 weeks were 12, 6, 6 and 12 rats respectively.

^3H_2O (50 μCi) and ^{24}Na (20 μCi) were given by tail vein injection 24 hours before sacrifice and rats transferred to metabolic cages for urine collection. On the day of operation, under ether anesthesia, a plastic sampling catheter was placed in the inferior vena cava of each rat at laparatomy. The sulfate-35 tracer was injected via the tail vein 30 min pre-sacrifice. Blood samples (1.5 ml) were collected at 0, 5, 10, 15, 20, and 30 minutes. Sodium-24 was permitted to decay (one week) before the other isotopes were counted.

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Volumes of distribution of ^{24}Na and ^{3}H were calculated from appropriate plasma and urine specimens. The zero time extrapolation of plasma $^{35}SO_4$ was used to measure ECW [24].

Rats were sacrificed after the sample collection. About a gram of femoral muscle, the femoral bone, and the brain were removed from the carcass. Electrolyte extractions and measurements were carried out as previously described [25]. The carcass was weighed and autoclaved for ten minutes and weighed, and then homogenized for ten minutes with an equal volume of ion free water. Dehydration weight was measured after two days in a 95°C oven. This data was used to confirm the TBW measured by $^{3}H_2O$. Electrolytes were extracted with 2N HNO_3 and measured as previously described [25]. Electrolyte contents (Na^+, K^+, Li^+, Ca^{++} and Mg^{++}) in RBC and serum were also measured by AA spectrophotometry. Means with one standard deviation of data are illustrated in figures and in tables. Differences between groups were considered statistically significant when p values were less than 0.05.

RESULTS

All data on food and fluid intake were measured per cage, with 1, 2, 3, or 4 rats housed in each cage. Individual data are given as the group mean when more than one rat occupied a cage.

Lithium was associated with a 20% ($p<0.10$) decrease in food and fluid intake. Alcohol was associated with a 38% ($p<0.001$) decrease in water intake, and a 48% ($p<0.001$) decrease in food intake, when compared with control animals, a finding which conforms with our previous study [26]. The combination of lithium and alcohol resulted in a 48% ($p<0.0001$) decrease in water, and a 59% ($p<0.0001$) decrease in food intake respectively. Since the 48% decrease in fluid intake in the Li-alc cohort was less than the predicted 66% decrease, and a 20% decrease in fluid intake occurred in rats taking lithium alone, the latter group took 6.5 mg/day (0.9 mM) while rats on alcohol-lithium combination took 11.2 mg/kg/day (1.6 mM) of lithium. These differences in dosing were recorded by the end of the second week, and consistently maintained through the nine week study.

Figure 1 shows the means and standard deviations of rats weight in grams at each week. Both rat cohorts taking lithium reached a peak of weight at five weeks followed by a slight decline, at a time when control animals were still gaining slightly. At nine weeks, average weights were 92%, 88%, and 70% of control animal weights in the alcohol, Li^+, and combined dosage regimens respectively.

TBW by $^{3}H_2O$ averaged 73.1±2.7% of weight, while the dessication method gave 67.2±1.1% of weight, the methodological difference being 8.1%, the paired $p<0.0001$. Since slight overmeasurement of water occurs because of H^+ exchange beyond the water pool, the dessication results are used in subsequent calculations.

TBW, extracellular water, Na_e^+ and intracellular Na_e^+ measured at 9 weeks are summarized in Table 1. The Na_e^+ changes were marked, and were highly significant, as shown in Fig. 2; Na_e^+ in controls remained stable at 2, 5, and 9 weeks, but both alcohol and Li^+ dosing were associated with Na_e^+ increases which were most marked when the drugs were combined ($p<0.0001$). The increase was principally in the intracellular space. The combined groups showed an increase in Na_i by 87%. Differences between groups in TBW, ECW, and ICW were not significant.

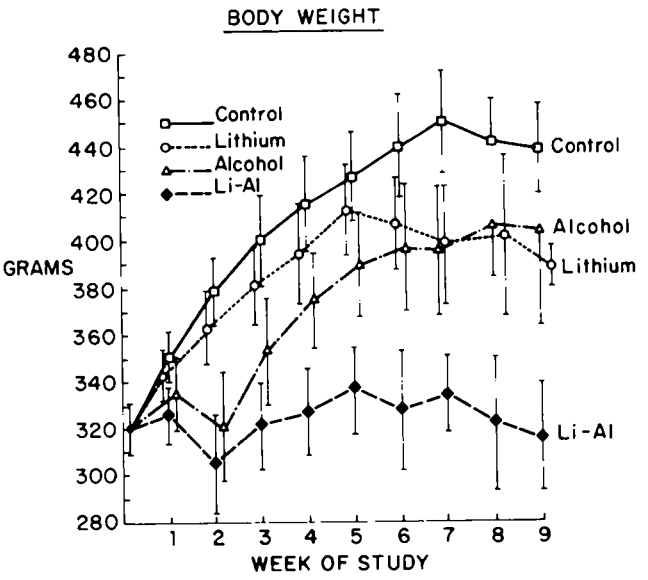

FIG. 1. Growth curves in controls, and in each study cohort during nine week study; means and one standard deviation. Significances are given in text.

TABLE 1

BODY COMPOSITION STUDIED AT 9 WEEKS

Study groups	Body water as % body weight				Na_e	
	TBW	ECW	ICW	E/I	Space % Body Wt.	(Na)i mEq/l
Control						
$\bar{x}$	66.2	20.3	45.9	0.44	34.1	36.9
S.D.	2.4	2.7	2.5	0.09	1.6	3.9
n=12						
Li						
$\bar{x}$	67.4	20.7	47.5	0.42	45.7*	63.3*
S.D.	1.5	2.5	4.0	0.03	3.1	4.0
n=8						
Alc						
$\bar{x}$	66.6	20.7	45.7	0.45	41.5*	55.2*
S.D.	1.1	3.1	3.0	0.06	4.4	6.3
n=7						
Li + Alc						
$\bar{x}$	68.4	18.7	49.7	0.38	49.9*	69.1*
S.D.	1.3	1.6	4.4	0.04	3.8	5.8
n=6						

*p value <0.0001 representing difference from control value.

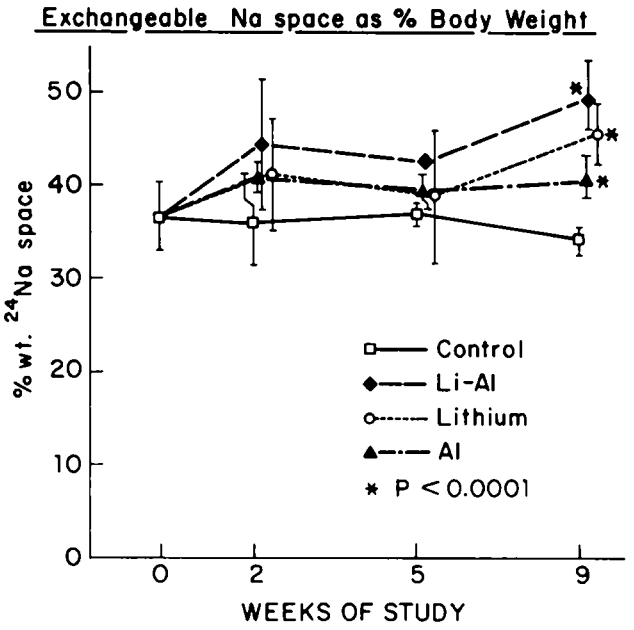

FIG. 2. Exchangeable Na as percent body weight in controls and in each study cohort; significant differences are seen at 9 weeks.

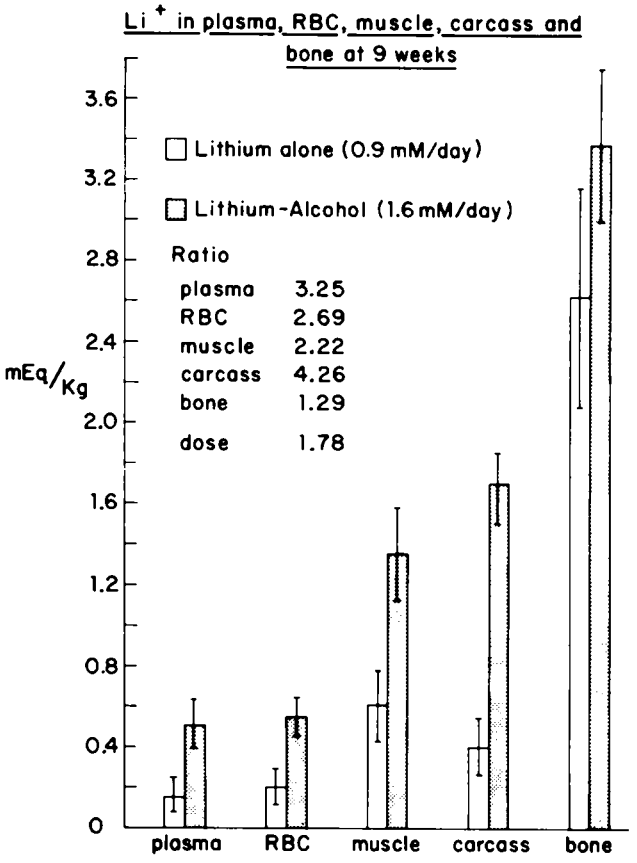

FIG. 3. Li^+ content in plasma and tissues at 9 weeks. The ratios of Li^+ content compare values in the cohorts taking Al and Li^+ to those taking Li^+ alone. Note that the dose ratio was 1.78.

Tissue Lithium Content

Lithium levels in plasma, RBC, muscle, bone and carcass as mEq per kg of fresh weight are summarized and compared for Li^+-alcohol and Li^+-only animals in Fig. 3. The Li^+ dose in the Li^+-alcohol rats was 72% greater than in the lithium cohort, due to an unanticipated difference in fluid intake. The ratios between the Li^+ contents in the various tissues of these two cohorts ranged from 1.29 in bone to 4.26 in the carcass. In Li^+-alcohol rats, in all tissues other than bone, lithium contents were highly significantly in excess of the dose ratios ($p<0.001$).

Muscle Electrolytes

Figure 4 shows the combined effects of Li^+ and alcohol on calcium, sodium, and potassium content in muscle measured as mEq/kg fresh weight. Early time points at two and five weeks showed fluctuation, but also showed trends which by nine weeks achieved statistical significance in the Li^+alcohol cohort:

Ca^{++}:37.0 ± 7.8% increase ($p<0.05$);
Na^+: 23.1 ± 3.7% increase ($p<0.02$); and
K^+: 14.1 ± 0.9% decrease ($p<0.002$)

Lithium alone and alcohol alone were associated with less marked changes, which achieved significance only in the case of decreased K^+ with Li^+ ($p<0.002$), but the directions of change were the same as those measured in the combined protocol. Since the ECW space remained at 21% by weight with each of the drug protocols, the ECW/ICW ratio was not altered by treatment. The lack of change of serum (and therefore ECW) Ca^{++}, Na^+, and K^+ levels indicates that the changes in muscle electrolytes were intracellular.

TABLE 2
ELECTROLYTE CONTENT IN CARCASS AT NINE WEEKS

	Ca^{++}	Mg^{++}	Na^+	K^+	Cl^-	K/Na
	g/100 g		mEq/kg Fresh Weight			
Control	1.08	0.044	52.6	88.0	28.2	1.67
S.D.	±.14	±.003	±4.4	±5.4	±1.3	
n=12						
Alcohol	1.02	0.048	60.4	90.5	29.2	1.50
S.D.	±.21	±.003	±10.9	±6.7	±5.9	
n=7						
Lithium	1.17	0.048	57.0	85.4	29.4	1.50
S.D.	±0.02	±.008	±2.5	±3.5	±2.5	
n=8						
Alc & Li^+	1.34	0.049	60.1	88.7	28.1	1.48
S.D.	±0.06	±0.004	±10.6	±6.5	±3.3	
n=6						

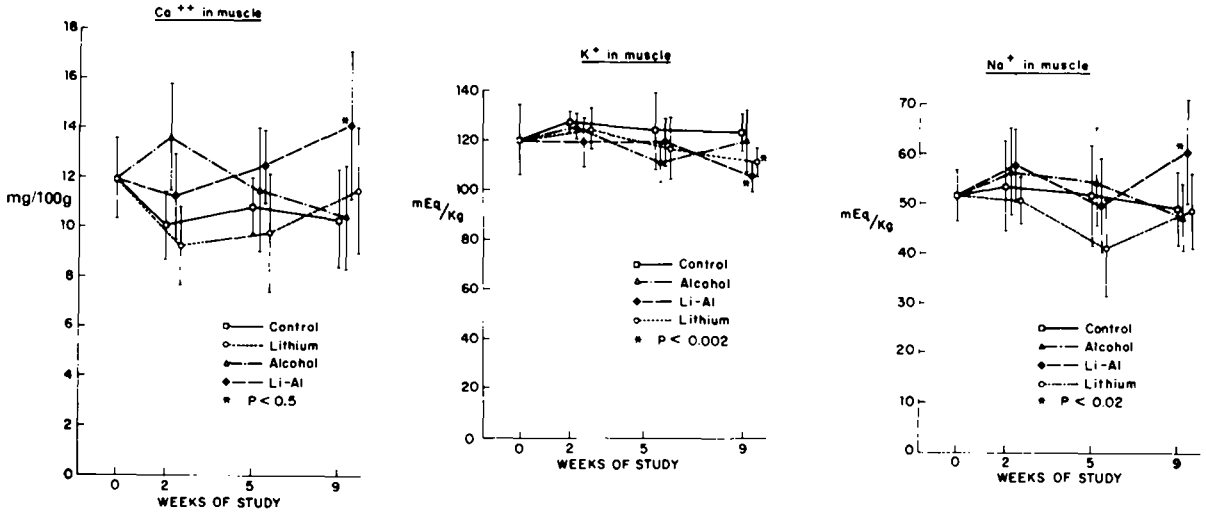

FIG. 4. Ca^{++}, K^+, and Na^+ content in skeletal muscle at 2, 5, and 9 weeks, in control and study cohorts. All show significant differences at 9 weeks in the alcohol and lithium cohorts.

Carcass Electrolytes

Table 2 summarizes the carcass electrolyte contents. No individual measurement was significantly different from the control cohort. The K/Na ratio was decreased in all treatment groups to a similar degree (11%), a change consistent with those measured in individual tissues. The marked weight differences between cohorts (Fig. 1) indicates that fresh weight may be an inappropriate denominator, since electrolyte content of individual tissues do show significant differences. Therefore analysis was also carried out using K^+ content as the denominator as summarized in Table 3. In every instance, Ca^{++}: K^+ ratios in muscle were higher in the study than in control groups ($p<0.05$). The Ca^{++}: K^+ ratio in the Li^+-alcohol group was still higher ($p<0.001$).

Bone Electrolytes

Figure 5 shows measurements of Ca^{++} and Na^+ in bone. As in muscle and carcass, trends established at the five week time point in most instances became more significant at nine weeks. Ca^{++} decreased by 839±52.5 mEq/kg of bone, or 8.7±0.03% ($p<0.05$), in the Li^+-alcohol cohort. Na^+ also decreased in this group, by 63.5±17.0 mEq/kg, or 26.4±7.1%,

TABLE 3

ELECTROLYTE AND WATER CONTENT PER GRAM OF POTASSIUM IN CARCASS AND IN MUSCLE MEASURED AT 9 WEEKS

		Carcass				Muscle	
Study groups		Ca^{++}/K^+ (g/g)	Na^+/K^+ (g/g)	TBW/K^+ (ml/g)	ECW/K^+ (ml/g)	Ca^{++}/K^+ (mg/g)	Na^+/K^+ (g/g)
Control		3.27	0.37	200.0	81.8	21.5	0.24
	S.D.	0.42	0.03	8.4	6.2	4.5	0.04
	n=12						
Li^+		3.52	0.39	202.8	88.8	26.4*	0.26
	S.D.	0.36	0.03	8.9	9.9	5.1	0.04
	n=8						
Alc.		3.42	0.39	196.3	81.8	22.4	0.23
	S.D.	0.04	0.04	26.8	6.2	5.2	0.03
	n=7						
Li^+-Alc.		3.90	0.40	198.8	82.1	34.5†	0.34†
	S.D.	0.35	0.07	11.5	12.3	8.8	0.06
	n=6						

*$p<0.05$.
†$p<0.001$.

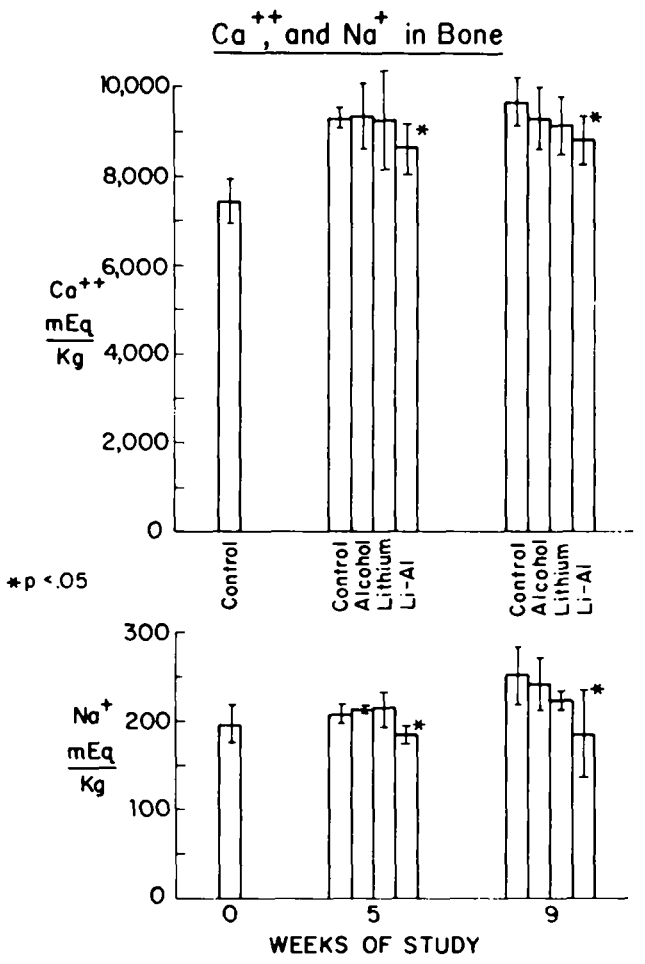

FIG. 5. Bone content of Ca^{++} and Na^{+} at 5 and 9 weeks. The Li^+ and alcohol cohorts showed significant depletions at both 5 and 9 weeks.

($p<0.05$). The ratio of Ca^{++} to Na^+ depletion was 13.7. The molar ratio of Ca^{++} to Na^+ in normal bone was 38.9 in our controls, a ratio which has been consistently found by others [1].

Bone contained the highest lithium concentration as shown in Fig. 3. Due to the higher Li^+ dosing of the Li^+-alcohol cohort, the difference in bone Li^+ content between Li^+alone and Li^+-alcohol cannot be interpreted. However molar "displacement ratios" may be calculated:

	Ca^{++} by Li^+	Na^+ by Li^+
Li^+-alcohol rats	247:1	18:1
Li^+-alone rats	203:1	10:1

DISCUSSION

Three methodologic problems appear to interfere with interpretation of this study in the most direct manner. These are, first, differences in lithium dosage between Li^+ and Li^+-alcohol cohorts; second, dehydration may have resulted from the aversive effects on fluid intake of 20% ethanol; and third, protein-mineral undernutrition may have resulted from toxic effects of lithium, or from dehydration.

Rats taking Li^+ alone consumed more water, and therefore more Li^+, than rats taking Li^+ in an ethanol solution. This failure in experimental design was a result very simply of the aversive effect of ethanol on water consumption, which might have been compensated by giving higher concentrations of Li-Cl to compensate for the lower fluid intake, had it been anticipated. As a result, the Li^+ alone group does not serve as quantitative control for the Li^+-alcohol group, and qualitative but not quantitative conclusions are drawn from this attempt to show a synergistic effect. All other comparisons with control levels are quantitative.

Dehydration might be inferred from decreased fluid intake in the experimental rats. However measurements of total water and extracellular water in these animals show no significant difference between cohorts, suggesting that any changes in total hydration were within the range of intrinsic homeostatic response mechanisms.

Weight gain with therapeutic Li^+ doses has been noted by many investigators in human studies recently reviewed by Birch [3]. In depressed humans, concomitant improvement in psychological status, motivation to eat, and actual food intake, suggested a therapeutic Li^+ effect. In rats, Opitz [15] has shown an inverse relationship between Li^+ dose and weight gain, with dosed rats always gaining less than matched controls, whether or not the dose administered resulted in Li^+ toxicity. Ramsey [17] noted that Sprague-Dawley rats are more sensitive to Li^+ than humans, developing toxicity at plasma levels below 1 mEq/l. Plasma Li^+ levels in our Li^+-alone rats were 0.16 ± 0.08, and in our Li^+-alcohol were 0.51 ± 0.12 mEq/l, bordering on the toxic range for rats in the case of Li^+-alcohol.

The minimum daily requirements for consumption of protein and major elements were calculated based on the consumption of the Li-alcohol groups, which consumed the smallest amount of chow. These data are compared with the nutrient requirements of laboratory animals as published by National Research Committee, NAS, 1978. Even with the combined regimen, alcohol and lithium rats consumed more protein, calories, Ca^{++}, Na^+, and K^+ than that of the standard required. We therefore believe that changes observed in the body composition of the study groups are not due to deficiencies of these elements.

Our finding of anorexia associated even with the lowest (and by all criteria sub-toxic) levels of plasma Li^+ confirm the findings of Frazer [6]. Mortality of 13% in our Li^+-alcohol group provides further evidence of Li^+ toxicity at these dose levels.

Li^+ Retention

Human investigation shows a non-linear relationship between dose and plasma level, and dose and toxic effect, indicating a binding saturation effect [10,18]. The additive effect of alcohol in this system has not of course been thoroughly explored in this study, in which only a single level of Li^+ and alcohol was evaluated. However as an exploratory probe of possible additive effects, it is sufficient to establish that "biologically reasonable" levels of alcohol and Li^+ were used. Our alcohol dose level is a standard and well-studied protocol which achieves approximately 33% of calories as alcohol, a level generally accepted as matching that in human alcoholism [26]. In our additive cohort, calories as alcohol

increased to 38% of total calories. Under this circumstance, Li^+ retention in the combined cohort compared with the Li^+-alone control group for all organs except bone; the enhanced Li^+ retention when alcohol was given exceeded very significantly the ratio of Li^+ dosage in tissue Li^+. Ho and Ho have also reported a lithium retention in ethanol treated rats [8]. We conclude from this particular set of data (1) that the Li^+ levels come too close to the toxic level for this species to consider that this result may be applicable in clinical situations; (2) that an additive effect occurs under these circumstances with alcohol enhancing Li^+ retention very significantly.

Additional conclusions may be of some interest: RBC Li^+ has been considered a readily available, and perhaps useful, index of intracellular Li^+. In this species it is not, reaching only about one third the level of that in skeletal muscle and carcass.

Effects on Na^+, K^+, and Ca^{++} in Tissues

Ethanol and Li^+ effects on water and electrolyte distribution have been reported by us [16] and by others [2, 7, 9, 20]. The current study demonstrates expansion of the exchangeable Na^+ by 50% with alcohol, by 72% with Li^+ alone, and an additive expansion of 95% with combined exposure. Since balance studies were not carried out, we cannot specify to what extent net Ca^{++} loss and Na^+ gain involved absorption and excretion. However it is clear that a new steady state involving increased tissue Ca^{++} and Na^+ is associated with these drugs, and that an additive effect occurs. Muscle Na^+ increased by 23%, indicating one repository for the liberated Na^+. Muscle K^+ decreased, maintaining the osmolality. This shift of Na^+ and K^+ may relate to the neuromuscular dysfunction we observed. We therefore believe that this finding may illustrate the side effect of Li^+ to alcoholics. The highest mortality (13%) in the Li^+-Alcoholic rats confirms a study by Ho *et al.* that the LD_{50} decreased by 30 to 44% in ethanol treated mice [8].

The total body water content and its distribution between the intra and extra cellular space were similar in all of the groups, when normalized for body weight. The observed changes in Na_e^+ in the study groups therefore were not due to the decreased body weight.

Toxic Effects

Dry and rough skin, erythema, and yellowing of fur color, were noted most severely in the combined group, but were also present in the alcohol and lithium cohorts. Wheezing, broken teeth, tremor, and gait disturbances were noted in Li^+ alone, and much more severely, in Li^+-alcohol cohorts, but not with alcohol alone. All of the abnormalities appeared between the fourth and fifth weeks, and were progressive, being most severe in the four rats dying during the study. Deaths occurred between the sixth and ninth weeks in one of eight rats on alcohol alone, and in two of eight rats on Li^+-alcohol combined.

Ethanol or Lithium Preference, and Dehydration

Food and fluid were given ad lib throughout the study. During the second and seventh weeks, half the study rats were tested for ethanol and lithium preference by substituting tap water for drug solution for 24 hours. All rats thus tested responded by consuming about twice the fluid volumes compared with ethanol and lithium solutions on preceding and succeeding days, indicating an aversion by Sprague-Dawley rats for ethanol and lithium.

Reduction in food intake paralleled reduction in fluids in all experimental groups. Thus rats may have avoided dehydration by reducing intake of solids. Measured TBW, ECW, and ICW were not significantly different between groups; thus dehydration was excluded as a possible toxic effect of drug administration.

In summary, both Li^+ and alcohol caused a decrease in bone Ca^{++}, and released a portion of bone-bound sodium, which became exchangeable to tracer sodium. A portion of the liberated sodium was found in the intracellular space in muscle. Potentiation of the Na^+ liberating effects of alcohol occurs with Li^+. Although Na^+ shifts markedly, from bone to cellular sites, the ECW and ICW remained normal.

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