Pharmacology Biochemistry & Behavior, Vol 10, pp. 933–935 Printed in the U S.A.

Dissimilar Effects of Lithium Isotopes on Motility in Rats

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(Received 3 February 1979)

LIEBERMAN, K. W., G. J. ALEXANDER AND P. STOKES. *Dissimilar effects of lithium isotopes on motility in rats.* PHARMAC. BIOCHEM. BEHAV. **10**(6) 933–935, 1979.—Male Wistar rats were injected twice daily with chlorides of pure lithium isotopes, either Li-6 or Li-7. While both salts decreased motility, the salt of Li-6 initially produced a more profound effect than the salt of Li-7. This differential effect of the isotopes proved to be time dependent and was most evident on the third day of treatment. Li-6 is likely to become a valuable tool in basic psychopharmacological research. It may possess therapeutic and/or toxic properties that are different from those of lithium salts currently used in treatment of mania.

Lithium Isotopes Lithium-7 Lithum-6 Motility

LITHIUM is effective in the treatment of mania [2], but the underlying pharmacological mechanisms responsible for its action remain obscure. There are two naturally occurring stable isotopes of lithium, Li-7 is the more abundant isotope (92.6%) and Li-6 is the minor constituent (7.4%) [4]. Usually there is little differentiation between the isotopes of an element either physiologically or chemically, but lithium is an exception. As a consequence of its small atomic weight the mass difference between Li-6 and Li-7 is comparatively large: only the three isotopes of hydrogen have larger mass differences. We have previously reported in a study of the *in vivo* and *in vitro* uptake of the two lithium isotopes that more Li-6 than Li-7 entered human erythrocytes during the initial few hours of exposure to the isotopes [8,12]. The biological activity of pure Li-6 may differ from that of the common lithium salts used clinically, which are predominantly Li-7.

Spontaneous motor activity of experimental animals is known to decrease after treatment with lithium. Rats given the naturally occurring mixture of isotopes of lithium for up to ten days showed a significant decrease in exploratory behavior and motility [5, 7, 9, 11]. To the best of our knowledge there are no prior reports of any behavioral effects of isotopically pure salts of lithium.

We have administered Li-6 and Li-7 to rats and found that while both isotopes decreased motility, Li-6 initially produced a more profound effect than Li-7. This differential behavioral effect of the isotopes proved to be time dependent: it was most evident on the third day of treatment and disappeared by the fifth day.

METHOD

Thirty male Wistar rats (280 ± 40 g) were divided at random into three equal groups. Group 1 received intraperitoneal injections of aqueous Li-6 chloride (1.5 mEq/kg, 1 ml/kg) twice a day at 9 a.m. and 4 p.m. and once at 9 a.m. on the fifth day. Group 2 received a parallel course of injections of Li-7 chloride utilizing the same dosage schedule as Group 1, and Group 3 (controls) received placebo (distilled water). Li-6 and Li-7 chlorides were purchased from Oak Ridge National Laboratories, Oak Ridge, Tennessee where the isotopic purity was determined to be greater than 99% for both Li-6 and Li-7 chlorides. Motility was tested daily at 11 a.m. and 3 p.m. in a Motility Tester (Model 80, Bel Art Corp., Pequannock, N.J.) activated when the animal crossed from one plate to another completing a weak electric circuit and was recorded as the number of crossings in a fifteen minute period. Differences in motility between the morning

TABLE 1

EFFECT OF TREATMENT WITH Li-6 OR Li-7 ON MOTILITY AND BLOOD LITHIUM LEVELS

Group	Motility (crossings/15 minutes)				Blood Li (meq/l), Day 5	
	Pretreatment	Day 3	Day 4	Day 5	Erythrocytes	Plasma
Control	36.3 ± 5 4	41.8 ± 21 0	43 5 ± 10.9	34 1 ± 10 3	—	—
Li-7	38 6 ± 11.6	31.8 ± 23 9	25 5 ± 18 9	14 0 ± 7 2	0 90 ± 0.10	0 98 ± 0 12
Li-6	41.2 ± 10 1	21 5 ± 15.4	14 9 ± 10 9	15 6 ± 12 0	1 02 ± 0 23	1 18 ± 0 32

Values are given as ± standard deviations

and afternoon readings were minimal and values were averaged for each day. Baseline motility was obtained during a two week period prior to lithium administration. At noon on the fifth day the rats were sacrificed and blood samples collected. Erythrocytes were separated from plasma by centrifugation and the concentrations of Li-6 and Li-7 in the separated fractions determined by atomic absorption spectrophotometry after corrections were made for plasma entrapped with cobalt-60 ethylenediaminetetraacetic acid as an extracellular marker [3].

RESULTS

Gross observations of behavior revealed that while motility within each group of ten varied widely leading to a high standard deviation which is frequently encountered in this type of experiment, the motility of the individual animals treated with either lithium isotope as well as the group mean of lithium animals decreased with time. Animals in the group treated with Li-6 appeared to experience a more rapid decrease than the corresponding animals in the Li-7 group.

These observations were confirmed with quantitative measurements in the Motility Tester. Pre- and post-treatment values for each animal were compared. In addition, animals within each treatment group were ranked according to their pre-treatment motility. These motility results were analyzed for statistical significance using a two-tailed Student t test for groups of paired data, pairs consisting of animals of equal rank.

On the third day the mean motility of the Li-6 group was 52% ($p<0.02$) and the mean motility of the Li-7 group was 82% ($p<0.05$) of the pre-treatment value. Also, on the third day the differences between ranked paired animals in the Li-6 group and the corresponding animals in the control group were statistically significant ($p<0.02$). Of possibly greater interest was the difference in motility on the third day between ranked pairs of Li-6 and Li-7 animals, which was significant at a confidence level of $p<0.05$. On the fourth day, motility was reduced 64% in the Li-6 group and 34% in the Li-7 group compared to pre-treatment values. The Li-6 group was significantly less active than the Li-7 group on the fourth day ($p<0.05$)

On the fifth day both groups that were given lithium isotopes were less active than prior to treatment; the mean reduction was 62% for Li-6 and 64% for Li-7. The effect of Li-7 on motility after five days of treatment was not significantly different from that of Li-6

Blood lithium analyses indicated that on the fifth day the concentration of Li-6 was greater than Li-7 in both erythrocytes and plasma with more of either isotope in the plasma than in the corresponding erythrocytes.

DISCUSSION

With Li-6 and Li-7 we have demonstrated that isotopes of the same element can produce quantitatively different behavioral effects and that Li-6 attains higher erythrocyte and plasma values *in vivo* and *in vitro* than Li-7 [8,12]. Li-6 may possess therapeutic and/or toxic properties that are different from Li-7, the major component of naturally occurring lithium. In fact, work in progress shows Li-6 to be more toxic than Li-7 in mice (manuscript submitted). We suggest that Li-6 is likely to become a valuable tool in basic psychopharmacological research and as a tracer in elucidating the mechanism of action of lithium as an antimanic drug. The potential clinical usefulness of Li-6 needs to be further explored.

ACKNOWLEDGEMENT

We thank Arlene Nadolski for her extensive assistance with the isotopic lithium analyses and Steve Sands for his help with the motility measurements This work was supported in part by the George Baker Trust

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