Plasma and Brain Lithium Levels After Lithium Carbonate and Lithium Chloride Administration by Different Routes in Rats (35687)

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(Introduced by J. T. Litchfield)
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The current interest in the use of lithium for the treatment of mood disorders has stimulated interest in its pharmacologic actions. Lithium is usually given as the carbonate in therapy, but the only major study of the absorption and distribution of lithium was carried out with iv lithium chloride (1). The present study in rats was designed to examine the absorption of the lithium ion into the blood and its distribution between blood and brain after single oral and ip doses of lithium chloride and lithium carbonate.

Methods. Male Wistar rats (Rockland Farms), weighing 200–400 g were used in this study. They were housed in FDA animal quarters with constant temperature and humidity and a diurnal lighting cycle. The rats were given free access to food and water throughout the experiment. Lithium chloride in a 0.9% saline solution and lithium carbonate in a 0.5% carboxymethylcellulose suspending medium were administered in doses of 0.0, 2.5, 5.0, 10.0, and 20.0 mEq of lithium per kg of body weight. This dose range encompasses that of most other animal experiments which run from about 2.5 to 15 mEq/kg (2), and the human dose range of 0.8–3.6 mEq/kg (3, 4). Each drug was given ip or orally to separate groups of 3–9 rats at each dose level and time period. These animals were killed at 15 and 30 min, and at 1, 2, 4, 8, 12, 24, and 48 hr after the administration of the drug. Rats were killed by decapitation, blood was collected by exsanguination into heparinized tubes; brains were quickly removed, washed free of blood, and stored frozen until lithium analysis was performed. Blood samples were centrifuged at 1800 rpm, and the plasma was collected and refrigerated until lithium was analyzed. Lithium analysis was carried out by flame photometry using a Technicon AutoAnalyzer and the method of Nevius and Lanchantin (5). With this method there is virtually no interference from sodium or potassium and the sensitivity is 0.1 mEq/liter. A semiautomated method for brain lithium analysis based on the method of Schou (1), was developed and standardized and its specificity and sensitivity are the same as for the plasma method.

Results and Discussion. Plasma lithium levels after the ip and oral administration of lithium chloride and lithium carbonate are shown in Figs. 1 and 2. After ip administration peak lithium levels are usually reached more quickly after lithium chloride than lithium carbonate. The peak lithium levels reached after the two higher doses of lithium chloride are significantly greater ($p<.001$, t test) than the corresponding peaks obtained after lithium carbonate at the same dose levels. Plasma lithium levels after lithium chloride fall rapidly, and from 1 through 8 hr are lower than the plasma levels after lithium carbonate which decline in a linear fashion from 1 through 12–48 hr.

After oral administration, both compounds show similar absorption patterns with an increase in the first 15 or 30 min followed by a plateau at all dose levels that extends to 12 or 24 hr with no marked or consistent peaks in plasma levels. These plasma levels are higher than the levels found from between 8 or 12 and 24 hr after ip administration. After oral lithium carbonate plasma lithium levels are generally higher than those after oral

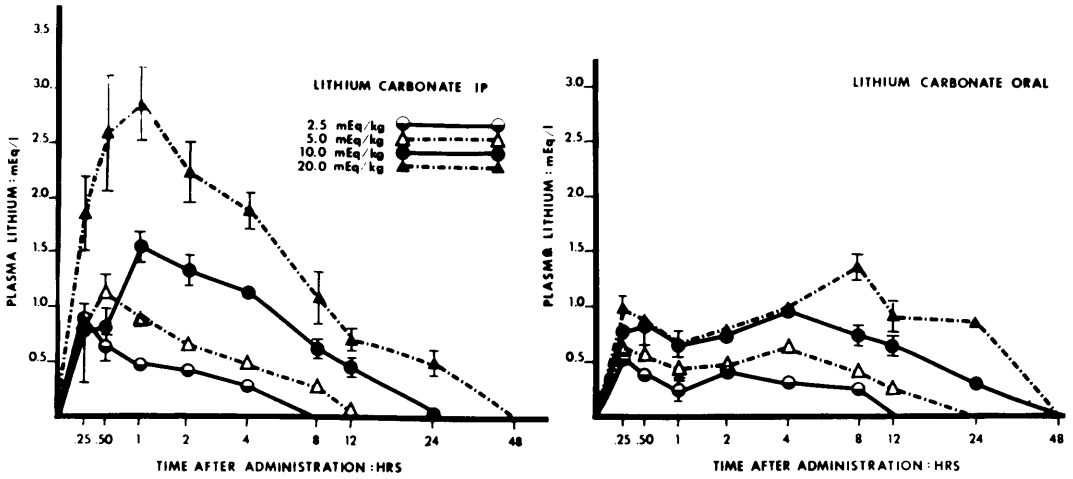

FIG. 1. Plasma lithium after ip and oral administration of lithium carbonate. The ordinate is plasma lithium in mEq/liter, and the abcissa is the time in hours on a logarithmic scale. Each point represents 3–12 determinations and the vertical bars are the standard error of the mean. Where vertical bars are not shown the standard error is less than 0.1 mEq/liter.

lithium chloride at all doses.

Brain lithium levels after lithium carbonate and lithium chloride are shown in Figs. 3 and 4. With both compounds and routes the lowest dose, 2.5 mEq/kg, gave brain lithium levels that were below the sensitivity of our method and have thus been omitted from the results.

After lithium carbonate ip brain lithium reaches measurable levels at 1 hr and rises irregularly to 8 hr where only the highest dose shows a discernible peak, and at which time the brain levels have become higher than the plasma levels. After oral administration of lithium carbonate, on the other hand, the brain levels at 1 hr are barely detectable and generally rise to reach a peak at 24 hr, with the brain concentration of lithium being greater than that of plasma at between 12 and 24 hr. The brain levels achieved after oral administration are significantly lower than those after the ip route at 20.0 mEq/kg

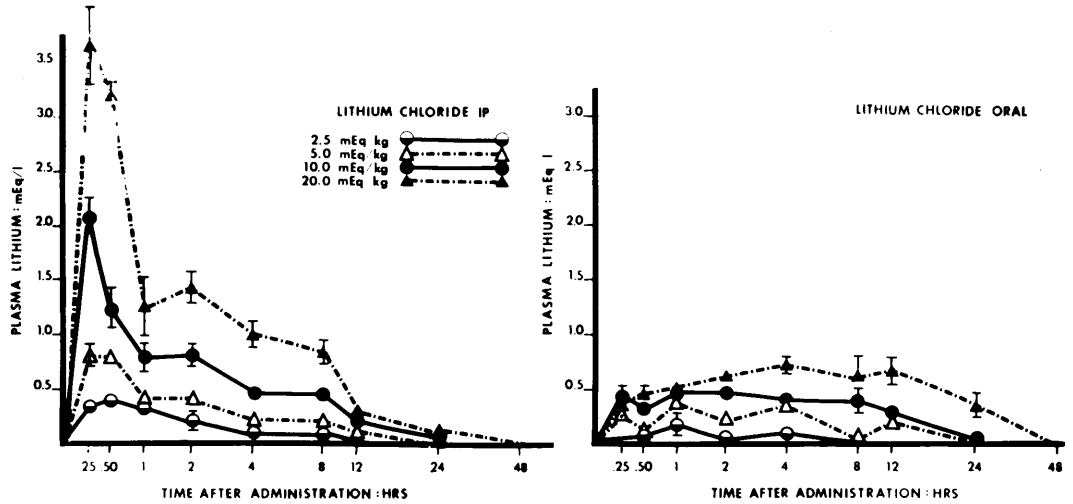

FIG. 2. Plasma lithium after ip and oral administration of lithium chloride. The ordinate and abcissa are the same as in Fig. 1.

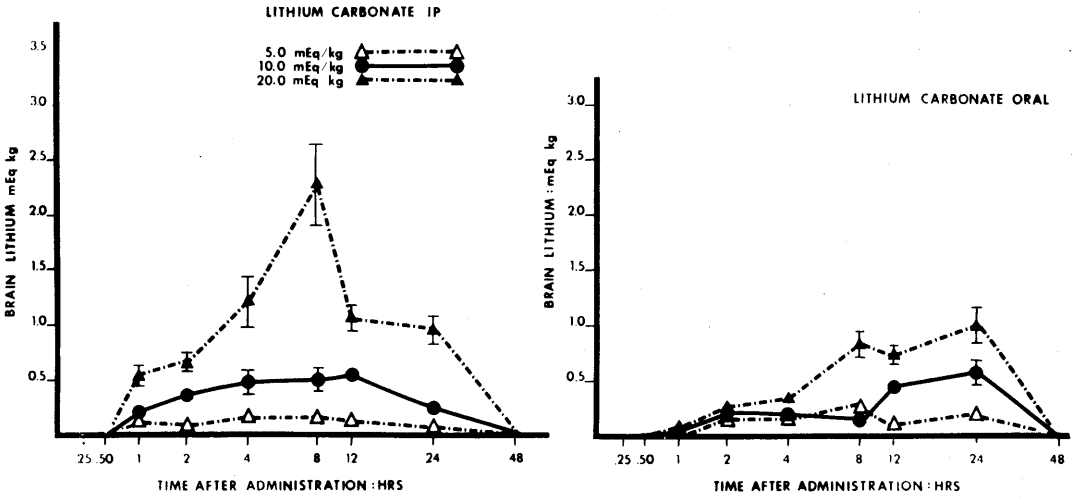

FIG. 3. Brain lithium after ip and oral administration of lithium carbonate. The ordinate is brain lithium in mEq/kg expressed on the same scale as plasma lithium, and the abcissa is the same as in Figs. 1 and 2.

dose but not at lower doses. In both cases the 5.0 mEq/kg dose gives levels that are quite low and variable and that seem to follow no pattern as do the two higher doses.

A similar picture is seen after lithium chloride with no discernible peak brain levels after ip administration and generally rising levels to 24 hrs after the oral route.

These absorption patterns are similar to that described by Schou (6) after iv lithium chloride, and demonstrate that the movement of the lithium ion into the brain is slow and that its efflux is slow as well. This would imply that relatively constant blood levels over a period of 24 hr or more would be needed before there is an equilibration between blood and brain lithium levels.

Summary. A study of the absorption and distribution of lithium carbonate and lithium chloride after oral and ip administration has shown that lithium chloride was absorbed more rapidly into the blood than lithium carbonate after ip administration, that lithium chloride given orally is absorbed to a lesser

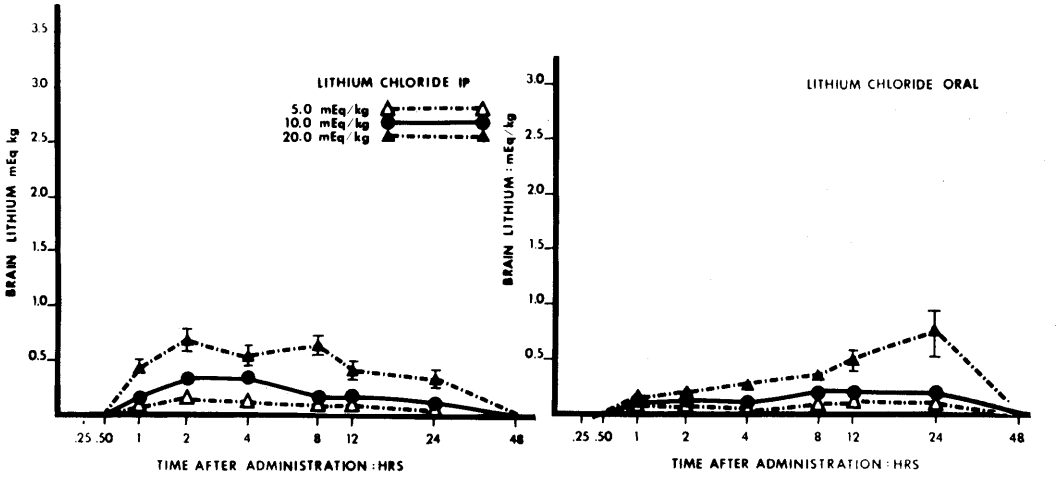

FIG. 4. Brain lithium after ip and oral administration of lithium chloride. The ordinate and abcissa are the same as in Fig. 3.

extent than lithium carbonate, and that the patterns of oral and ip absorption of both compounds are similar. We have also shown that the movement of lithium ions into the brain is slow, that only relatively low levels are achieved, and that the lithium brain levels are directly related to and dependant on the magnitude and duration of the plasma levels.

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