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LITHIUM OROTATE, CARBONATE AND CHLORIDE: PHARMACOKINETICS, POLYDIPSIA AND POLYURIA IN RATS

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1 The pharmacokinetics of the lithium ion administered as lithium orotate were studied in rats. Parallel studies were carried out with lithium carbonate and lithium chloride.

2 No differences in the uptake, distribution and excretion of the lithium ion were observed between lithium orotate, lithium carbonate and lithium chloride after single intraperitoneal, subcutaneous or intragastric injections (0.5–1.0 mEq lithium/kg) or after administration of the lithium salts for 20 days in the food.

3 The findings oppose the notion that the pharmacokinetics of the lithium ion given as lithium orotate differ from lithium chloride or lithium carbonate.

4 Polyuria and polydipsia developed more slowly in rats given lithium orotate than in those given lithium carbonate or lithium chloride, perhaps due to an effect of the orotate anion.

Introduction

Lithium orotate was recently introduced as a drug by Nieper (1973a) who used it in clinical trials in the hope of applying the principle of directed electrolyte transport in lithium therapy. His studies on calcium orotate and magnesium orotate indicated that these salts pass through the cell membrane in undissociated form and release the respective ions only at the site of membranes of cytoplasmic structures (Nieper, 1969; 1970; 1973b). Nieper assumed that lithium orotate also would be taken up in the undissociated form specifically into the tissues of the central nervous system whereupon the lithium ion would be liberated within the cells (Nieper, 1973a).

To date, no detailed information is available concerning the uptake, distribution and excretion of lithium orotate. The present study was carried out primarily to investigate the pharmacokinetics of the lithium ion when administered as lithium orotate. In addition, the effect of long-term administration of lithium orotate on water intake and urine output in rats was investigated. Parallel investigations were carried out with lithium carbonate and lithium chloride.

Methods

Male albino Wistar rats weighing 250–300 g were housed in a thermostatically controlled room (23°C) on a 12 h light-dark cycle (lights on 8 h 00 min to 20 h 00 min) with rat chow pellets and tap water freely available for at least 3 weeks before the experiments.

Short-term experiments

Serum lithium concentrations and urinary lithium excretion were studied in 9 rats given an intraperitoneal, subcutaneous or intragastric injection of 0.5 mEq lithium/kg body weight as 0.05 M lithium orotate (LiOr), 0.05 M lithium chloride (LiCl) or 0.025M lithium carbonate (Li_2CO_3) at 10 h 00 min. Blood samples were taken at 10 h 40 min and 14 h 30 min under ether anaesthesia from the rat tails. Urine was collected between 11 h 00 min and 14 h 00 min as described in detail previously (Smith, 1974). Each rat was tested 5 times at 3–4 day intervals and received a different treatment prior to each test. The lithium concentration in the serum and urine samples was determined by flame photometry (Amdisen, 1967).

The distribution of lithium was examined in 8 rats killed at 15 h 15 min, 7 h after an intragastric injection (1 mEq lithium/kg) of either 0.05 M LiOr or 0.025 M Li_2CO_3. The lithium concentration in tissues, red blood cells and plasma was determined by flame photometry (Schou, 1958; Amdisen, 1967).

Long-term experiments

Water intake, urine output and the distribution of lithium were studied in 16 rats randomly divided into 4

equal groups and given free access to wet mash diet (Thomsen, 1970) containing either no lithium or LiOr, Li_2CO_3 or LiCl for 20 days. The lithium concentration in the food was increased by 15 mEq/kg dry wt at 4 day intervals until the concentration of lithium was 60 mEq/kg dry wt; it was kept at this level thereafter. Tap water intake was measured daily. Blood samples were taken into heparinized tubes periodically under ether anaesthesia from the rat tails. On the 20th day, the volume of urine excreted by the rats was measured in individual metabolism cages without food or water present from 10 h 00 min to 14 h 00 min. The rats were killed thereafter and the lithium concentration in the tissues and blood was determined by flame photometry (Amdisen, 1967; Schou, 1958).

Results

Short-term experiments

The results presented in Table 1 show that the serum lithium levels and the amounts of lithium excreted in the urine obtained after intraperitoneal, subcutaneous or intragastric administration of LiOr did not differ significantly in any respect from the results obtained with Li_2CO_3 or LiCl. The serum lithium level 40 min after intragastric injection of the lithium salts was significantly less than after intraperitoneal or subcutaneous injections ($P < 0.05$). A significant decline occurred in the serum lithium level during the test after intraperitoneal or subcutaneous injections

Table 1 Serum lithium concentration at 40 min and 4.5 h postinjection and urinary lithium excretion from 1 to 4 h postinjection in rats given an intraperitoneal (i.p.), subcutaneous (s.c.) or intragastric (i.g.) injection (0.5 mEq lithium/kg body wt.) of lithium orotate, lithium carbonate or lithium chloride

		Serum lithium concentration (mEq/l)		*Renal lithium excretion (μEq kg^{-1} h^{-1})*
		40 min	*4.5 h*	
Lithium orotate	i.p.	0.40 ± 0.02	0.20 ± 0.03	30.0 ± 2.4
	s.c.	0.45 ± 0.02	0.23 ± 0.10	30.7 ± 5.1
	i.g.	0.28 ± 0.02	0.22 ± 0.02	31.4 ± 3.2
Lithium carbonate	i.p.	0.45 ± 0.03	0.21 ± 0.01	31.8 ± 5.7
	s.c.	0.52 ± 0.06	0.23 ± 0.03	31.4 ± 5.1
	i.g.	0.28 ± 0.01	0.22 ± 0.02	32.8 ± 4.6
Lithium chloride	i.p.	0.39 ± 0.04	0.18 ± 0.03	29.7 ± 5.2
	s.c.	0.44 ± 0.04	0.17 ± 0.02	30.2 ± 2.7
	i.g.	0.28 ± 0.05	0.20 ± 0.04	29.6 ± 2.3

Values are means ± s.d. for 5 rats

Table 2 Lithium concentration in blood and tissues 7 h after a stomach load of lithium orotate or lithium carbonate (1 mEq/kg body wt.)

	Lithium concentration (mEq/kg wet wt; mEq/l)	
Tissue	*Lithium orotate*	*Lithium carbonate*
Brain (whole)	0.11 ± 0.03	0.10 ± 0.01
Liver (middle lobe)	0.12 ± 0.01	0.11 ± 0.01
Muscle (gastrocnemius)	0.20 ± 0.01	0.19 ± 0.01
Lung	0.22 ± 0.02	0.22 ± 0.02
Heart (whole)	0.27 ± 0.03	0.29 ± 0.01
Red blood cells	0.36 ± 0.05	0.32 ± 0.08
Kidney	0.36 ± 0.05	0.37 ± 0.06
Plasma	0.44 ± 0.04	0.44 ± 0.03

Values are means ± s.d. for 4 rats.

($P < 0.05$). The route of administration of LiOr, Li_2CO_3 and LiCl had no significant effect on the amount of lithium excreted in the urine.

The results presented in Table 2 show that the concentration of lithium in the blood and tissues in rats given LiOr did not differ significantly in any respect from the levels obtained in animals given Li_2CO_3. Lithium was not uniformly distributed throughout all tissues after short-term administration; the lowest concentrations were obtained in the brain and liver and the highest levels were in the plasma and kidney.

Long-term experiments

The data in Table 3 show that the plasma lithium concentration in rats given LiOr in their food did not differ significantly in any respect from the groups given Li_2CO_3 or LiCl in their food. As the concentration of lithium in the food was increased, the plasma lithium concentration rose similarly in all the groups.

The data in Table 4 show that the concentration of lithium in the blood and tissues in rats given LiOr in their food did not differ significantly in any respect from the levels obtained in animals given Li_2CO_3 or LiCl in their food. Lithium was not uniformly distributed throughout all tissues after long-term administration; the lowest concentrations were obtained in the liver and the highest levels were in the kidney and muscle.

Figure 1 shows that the water intake increased significantly above control values in all groups given lithium; it was significantly higher than control levels after 9 days of treatment in rats given Li_2CO_3 or LiCl ($P < 0.05$), while 12 days of treatment with LiOr were required to produce a statistically significant ($P < 0.05$) increase in water intake. Within the experimental period, the water intake in rats given LiOr did not reach the level obtained in animals given Li_2CO_3 or LiCl.

Table 3 Plasma lithium concentration during long-term administration of increasing concentrations of lithium orotate, lithium carbonate or lithium chloride in the food

		Plasma lithium concentration (mEq/l)		
Lithium concentration in food (mEq/kg dry wt)	*Days*	*Lithium orotate*	*Lithium carbonate*	*Lithium chloride*
15	1–4	0.23 ± 0.03	0.21 ± 0.01	0.22 ± 0.02
30	5–8	0.38 ± 0.03	0.34 ± 0.03	0.38 ± 0.02
45	9–12	0.47 ± 0.04	0.52 ± 0.04	0.48 ± 0.07
60	13–15	0.54 ± 0.06	0.58 ± 0.06	0.51 ± 0.03

Values are means ± s.d. for 4 rats.

Table 4 Lithium concentration in blood and tissues after administration of lithium orotate, lithium carbonate or lithium chloride in the food for 20 days

	Lithium concentration (mEq/kg wet wt; mEq/l)		
Tissue	*Lithium orotate*	*Lithium carbonate*	*Lithium chloride*
Liver (middle lobe)	0.34 ± 0.07	0.30 ± 0.01	0.31 ± 0.08
Plasma	0.63 ± 0.11	0.65 ± 0.08	0.64 ± 0.07
Red blood cells	0.65 ± 0.06	0.68 ± 0.10	0.59 ± 0.09
Lung	0.67 ± 0.06	0.67 ± 0.11	0.58 ± 0.06
Brain (whole)	0.68 ± 0.05	0.67 ± 0.03	0.67 ± 0.08
Heart (whole)	0.74 ± 0.10	0.72 ± 0.04	0.70 ± 0.08
Muscle (gastrocnemius)	0.76 ± 0.12	0.78 ± 0.10	0.83 ± 0.13
Kidney	1.01 ± 0.21	0.92 ± 0.06	0.95 ± 0.04

The lithium concentration in the food was 60 mEq/kg dry wt. for the last 8 days of treatment. Values are means ± s.d. for 4 rats.

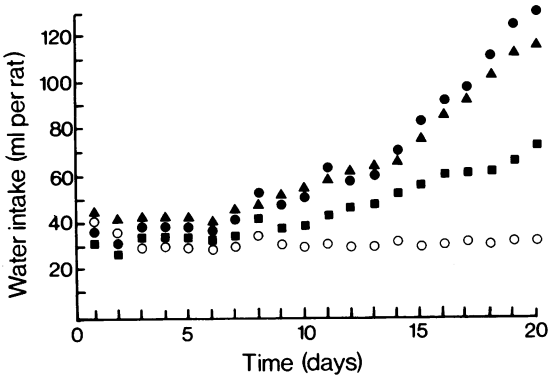

Figure 1 Mean daily water intake in rats given either no lithium (○) or increasing concentrations of lithium orotate (■), lithium carbonate (▲) or lithium chloride (●) in the food. The concentration of lithium in the food was 15 mEq/kg dry wt. from day 1 to 4, 30 mEq/kg dry wt. from day 5 to 8, 45 mEq/kg dry wt. from day 9 to 12, and 60 mEq/kg dry wt. from day 13 to 20.

On the 20th day, the control group excreted 3.5 ± 0.7 ml of urine during the test. The urine volume in the group given LiCl (11.1 ± 2.9 ml) was significantly greater ($P < 0.05$) than in the control group as well as in the group given LiOr (6.9 ± 3.0 ml). The urine output of rats given Li_2CO_3 (9.9 ± 4.1 ml) was significantly greater than the control level ($P < 0.05$) but did not differ significantly from the groups given LiCl or LiOr. The urine output in the control group and the group given LiOr did not differ significantly.

Discussion

No differences were observed between LiOr, Li_2CO_3 and LiCl in lithium absorption, distribution and urinary excretion after short-term or long-term administration. The features of lithium pharmacokinetics previously established using LiCl and Li_2CO_3, such as more rapid uptake of lithium after intraperitoneal injection than after intragastric administration (Morrison, Pritchard, Braude & D'Aguanno, 1971), higher lithium concentrations in serum than in brain soon after short-term lithium administration (Schou, 1958; Ebadi, Simmons, Hendrickson & Lacy, 1974), higher lithium concentrations in kidney and brain than in liver after long-term lithium administration (Birch & Hullin, 1972), and higher lithium concentrations in red blood cells than in plasma during prolonged administration of lithium (Smith, 1975) also were observed in the present study of LiOr. Thus, the findings offer no support whatsoever for the assumption that the pharmacokinetics of lithium ions given as LiOr differ from LiCl or Li_2CO_3 (Nieper, 1973a).

Polydipsia and polyuria occurred during long-term administration of LiOr, LiCl and Li_2CO_3. There was a tendency, however, for the onset of polydipsia and polyuria to be delayed during LiOr treatment compared to LiCl and Li_2CO_3; an unexpected finding since the pharmacokinetic studies showed no differences between the groups given LiOr, LiCl or Li_2CO_3 in the concentrations of lithium in blood and tissues. Although the mechanism responsible for the difference is not known, it might be due to an effect of the orotate anion.

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