CM20

(See rebuttal/comments by Hans A. Nieper, MD at the end of this paper)

Br. J. Pharmac. (1976), 56, 399-402

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

D.F. SMITH
Psychopharmacology Research Unit, Psychiatric Hospital, Risskov, Denmark

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 releases 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 250-300g were housed in a thermstatically 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 0.05M 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 (Thomas, 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 20^{th} 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 LiC1. The serum lithium level 40 min. after intragastric injection of the lithium salts was significantly less than after intraperitoneal or subcutaneous injections (P O. 05). A significant decline occurred in the serum lithium level during the test after intraperitoneal or subcutaneous injections ($P<0.05$). 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 give 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.

Table 1 Serum lithium concentration at 40 minutes 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 ($uEq\ kg^{-1}\ h^{-1}$)
		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

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_2Or_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.

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

Table 3.		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

Table 4.	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.

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.)

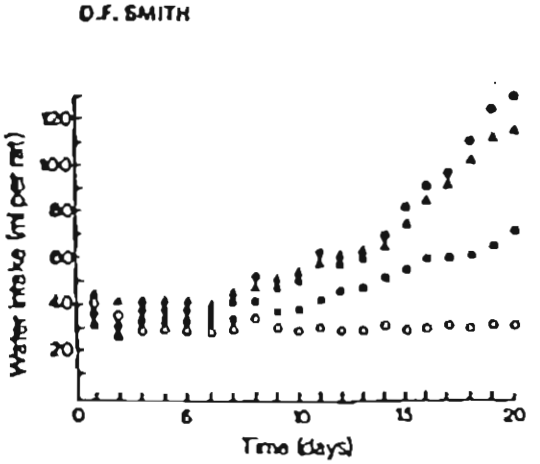
Table 2.

Tissue	Lithium concentration (mEq/kg wet wt; mEq/l) 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.

Figure 1 shows that the water intake increased significantly above concentration 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.

(Reference to Figure 1 below)
Figure 1 mean daily water intake in rats given either no lithium (●) or increasing concentrations of lithium orotate (■), lithium carbonate (▲) or lithium chloride (o) 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 5 to 8 , 45 mEq/kg dry wt. from day 9 to 12, and 60 mEq/kg dry wt. from day 13 to 20. Figure 1.



On the 20th day, the control group excreted 3.5 $\pm$ 0.7 ml of urine during the test. The urine volume in the group given LiC1 (11.1 $\pm$ 2.9 ml) was significantly greater (P 0.05) than in the control group as well as in the group given LiOr (6.9 $\pm$ 3.0 ml). The urine output of rats given Li_2CO_3 (9.9 $\pm$ 4.1 ml) was signifcantly 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 administion. The features of lithium pharmacokinetics previously established using LiCl and Li_2Co_3 such as more rapid uptake of lithium after intraperitonel injection than after intragastric administration (Morrison, Prichard, 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 concentration 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 supprt whatsoever for the assumption that the pharmacokinetics of lithium ions given as LiOr differ frm LiCl or Li_2Co_3, (Nieper, 1973a).

Polydipsia and polyuria occured 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.

The author thanks Nadrol-Chemie-Pharma, Osnabruck, Germany for the generous supply of lithium orotate: Mrs. Marianne Jensen for technical assistance: Aarhus University and Carl P. Petersens Fund for financial support.

REFERENCES

AMDISEN, A. (1967), Serum lithium determination for clinical use. Scand. J. Clin. Lab. Invest., 20 104-108

BIRCH, N.J. & HULLIN, R.P. (1972), The distribution and binding of lithium following its long-term administration. Life Science, 11, 1095-1099.

EBADI, M.S., SIMMONS, V.J., HENDRICKSON, M.J., & LACY, P.S. (1974) Pharmacokinetics of lithium and its regional distribution in rat brain. Eur. J. Pharmac. 27, 324-329

MORRISON, J.M. JR., PRITCHARD, H.D., BRAUDE, M.C. & D'AGUANNO, W. (1971). Plasma and brain lithium levels after lithium carbonate and lithium chloride administration by different routes in rats. Proc. Soc.exp. Biol., 137, 889-892

NIEPER, H.A. (1969). The anti-inflammatory and immune inhibiting effect of calcium orotate on bradytrophic tissue. Agressologie, 10, 349-354.

NIEPER, H.A. (1970) Recalcification of bone metastases by calcium diorotate. Agressologie, 11, 495-502.

NIEPER, H.A. (1973a) The clinical application of lithium orotate. A two year study. Agressologie, 14, 407-411

NIEPER, H.A. (1973b) Klinische Wirkung von Calcium-Diorotat auf Knorpelgewebe. Spezifische Funktion in Abhangigkeit vom Pentosen-Stoffwechsel bradytropher Gewebe. Z. Geriat., 3, 73-82.

SCHOU, M. (1958) Lithium studies. 3, Distribution between serum and tissues. Acta pharma. (Kbh), 15, 115-124.

SMITH, D.F. (1974) Renal lithium clearance during dehydration and rehydration with water or 0.9% NaCl in the rat. Acta physiol scand., 90, 427-430.

SMITH, D.F. (1975) Biogenic amines and the effect of short-term lithium administration on open field activity in rats. Psychopharmacologia (Berl.), 41, 295-300.

THOMSEN, K. (1970) Lithium-induced polyuria in rats. Int. Pharmacopsychiat., 5, 233-241.

Dr. Nieper's Comments on Research Report of D. F. Smith

July 1976-Hannover

The results reported by Smith are certainly most interesting especially with respect to the very restricted effect of lithium orotate to produce polydipsia and polyuria, compared to even serum concentrations of Li out of lithium carbonate and lithium chloride.

However, by expressing his interpretations of observed results in resorption and distribution essay, Smith revealed a few misunderstandings with respect to the mineral carrier concept which Laborit and I developed in the late 1950's, and which in the meantime became subject of some 2000 papers and also the basis for many drugs introduced into the market on the European continent and in Japan. (e.g. the K-mg-aspartates, the K, Mg, Ca-2-amino-ethylphosphates, an important series of orotates, etc.)

The compounds are not expected to fundamentally increase the concentration of particular minerals inside of cells but to free, upon their metabolization, a mineral to become an ion at very specific sites of cellular cell structures. The anionic carrier components must, therefore, dispose of the chemical property to form a high complex constant salt, and they must have a high affinity to particular cell systems as these should have the avidity for the compounds. Furthermore, the precise site of metabolization should be known. This is the outer layer of the cell membrane for the 2-amino-ethyl-phosphates, the inner layer of the outer cell membranes for the l-aspartates, and the mitochondrial, microsomal, and lysosomal membranes for the orotates which interestingly pass the outer cell membrane as a complex salt without being metabolized there.

The mechanism of action of the mineral carriers is mediated by the cytotopic release of the respective ions and their effect on particular enzymes or on topic mineral balances. The doses of mineral carriers needed for this effect are relatively small.

The explanation may outline why investigations of **plasma vs. cell** concentration of e.g. lithium orotate compared to lithium carbonate have little or no meaning. In addition to this only certain cell systems have a marked avidity to the orotates, namely mesenchymal tissue, and especially tissue based on pentose pathway metabolism such as glia.

How much the interpretation of experimental pharmacological findings can deviate from clinical reality may be demonstrated by the following: Smith says that there is no diffrence in the resorption and distributuion in rats between lithium orotate and lithium-carbonate or lithium chloride.

Clinically, however, the daily dose of Li-orotate in psychiatry is 300-450 mg. Doses of more than 600 mg. a day have no increasing therapeutic value. The Li serum level never gets higher than about 0.125 mval. Adverse effects of Li-orotate overdosage are headache and sometimes palpitation. They respond rapidly to a decrease of dosage, (just) as a desired therapeutic effect follows rapidly an increase of the dosage (20 h delay). Adverse effects of over dosage of Li-orotate are in no way related to the Li-serum level! Clinically, Li-orotate is furthermore active against migraine, juvenile convulsive diseases, episodic alcoholism, malignant lymphatic congestions and swellings, and especially against chronic aggressive hepatitis. Its ability to stabilize and dehydrate lysosomal membranes may also be of therapeutic benefit in the prevention of cardiac necrosis and arteriosclerosis.

In contrast to this, Li-carbonate, Li-chloride, and Li-acetate are in their effect mostly limited to the control of mania and bipolar depression. They are imposed with adverse effects like strumogenesis, polydipsia, and muscular fibrillation which are not known with the Li-orotate therapy. The effects on episodic alcoholism, first described by Nathan Kline, is less pronounced than with Li-orotate. Daily doses range for Li-carbonate and acetate from 0.8 to 2.5 g. per day, the serum Li-concentration should not be less than about 0.5 mval to assure a therapeutic effect. All these data differ, therefore, fundamentally from the values given for Li-orotate.

The therapy with Li-carbonate and Li-acetate make a repeated lab control of serum Li levels mandatory. In contrast to this, these controls have little meaning with the Li-orotate therapy.

Smith stresses the important superiority of Li-orotate over Li-acetate and Li-chloride in preventing polydipsia and polyuria even under the conditions of even serum concentration of Li. This of course would mean that under clinical therapeutic conditions Li-orotate would lack any adverse effects on the waterhousehold and also would possibly lack toxic effects on kidney function and structure which had been described for Li-carbonate.

The interpretations which Smith gives for this important finding is also erroneous: the very limited production of polydipsia by Lithium Orotate has nothing to do with orotic acid but is an expression of a very limited dissociation of Lithium Orotate in blood, in fact only 10-20 percent.

(Received June 2, 1975. Revised October 13, 1975.)

Additional comments on Lithium Orotate by Dr. Nieper:

With lithium orotate, we need only about 7% of the heretofore required amount of lithium, to achieve the desired effect. Dangerous involuntary functions such as muscle tremors, enlargement of the goiter and disturbances of the body water retention are drastically reduced. Above all, constant laboratory monitoring of the lithium level of the blood is no longer necessary.

Lithium orotate helps control not only depression and mania, but chronic inflammatory processes of the liver, and—according to research from Texas—with heart attacks and hardening of the arteries. The fundamental principle of the lithium effect is that it forces excess sodium out of the body cells.

Example:
One 120 mg. tablet of lithium orotate contains 4.6 mg of elemental lithium. To determine the appropriate dose if you have been taking lithium carbonate substitute one tablet of lithium orotate for each 100 mg of lithium carbonate. From four to twelve 120 mg tablets of lithium orotate may be used for alcoholism. From six to eight 120 mg tablets of lithium orotate may be used for depression. From two to three 120 mg tablets of lithium orotate may be used for migraines. It is important to seek the guidance of a physician to determine the optimum dose. The effective dose could be as little as one tablet a day.