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Kidney function and lithium concentrations of rats given an injection of lithium orotate or lithium carbonate

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A recent study by Kling et al (1978) noted the finding of higher lithium concentrations in serum and brain of rats after an intraperitoneal injection (2 mmol lithium kg^{-1}) of lithium orotate as a slurry than of lithium carbonate in solution. The authors suggested that lithium orotate might offer advantages in the treatment of patients. We repeated the experiments of Kling et al but in addition examined the kidney function of the rats. Glomerular filtration rate and urine flow were markedly lower in rats given lithium orotate than in rats given lithium carbonate, sodium chloride or a sham injection. The renal lithium clearance was significantly lower, the kidney weight and the lithium concentrations in serum, kidney and heart significantly higher after injection of lithium orotate than after injection of lithium carbonate. The higher lithium concentrations could be accounted for by the lower kidney function. It seems inadvisable to use lithium orotate for the treatment of patients.

Nieper (1973) recommended lithium orotate, $LiC_5H_3N_2O_4$, as a particularly useful salt for lithium treatment. He assumed that it passed cell membranes in the undissociated form and released lithium ions at intracellular target sites. This 'directed transport', he believed, would make lithium less toxic when administered in the form of lithium orotate.

Rat studies by Smith (1976) failed to demonstrate any differences between the uptake, the distribution, and the excretion of lithium whether it was administered as the orotate, the carbonate, or the chloride.

Recently, Kling et al (1978) repeated Nieper's assertion about the pharmacokinetic behaviour of lithium given as the orotate. They observed higher serum and brain lithium concentrations in rats after the orotate than after the carbonate. The authors suggested that the orotate might offer clinical advantages over the carbonate, because therapeutic brain lithium concentrations might be achieved with lower doses of the orotate.

We have considered it necessary to re-examine whether lithium orotate possesses pharmacokinetic properties that might render it preferable in treatment. We have therefore repeated the experiments of Kling et al, and in addition we measured the glomerular filtration rate and the renal lithium clearance of the rats.

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MATERIALS AND METHODS

Male albino Wistar rats, 350–370 g, were housed individually in a thermostatically controlled room (21 °C) on a 12 h light dark cycle (lights 6 a.m. to 6 p.m.) with free access to rat chow pellets and tap water for at least two weeks before the experiment. Injections were prepared as described by Kling et al (1978). Lithium carbonate (Merck) was dissolved in distilled water, the pH adjusted to 7·4 with HCl, and the final concentration was 200 mequiv lithium $litre^{-1}$. Lithium orotate (Nadrol-Chemie-Pharma) was prepared by dissolving 20 mequiv of lithium orotate in distilled water by heating and stirring. From this a fine precipitate formed on cooling to room temperature (21 °C). The pH was adjusted to 7·4 with NaOH, and the volume was adjusted to 100 ml. The resulting slurry was thoroughly and constantly stirred while portions were removed for injection, with 25 gauge needles, intraperitoneally into rats. As a control treatment, sodium chloride (Merck) was dissolved in distilled water, the pH was adjusted to 7·4 with NaOH, and the final concentration was 200 mequiv sodium $litre^{-1}$. As another control, rats were punctured intraperitoneally with a 25 gauge needle (sham treatment). The treatments were given at 9 a.m. to groups of 6 rats. At 10 a.m., the rats were anaesthetized with ether, and a blood sample (0·4–0·5 ml) was taken from the cut end of the tail. At 11 a.m., each rat was induced to empty its bladder and was placed in a metabolism cage with

only water available. At 2 p.m., each rat was again induced to empty its bladder, the volume of urine excreted during the 3 h clearance test was measured, and the inside of the metabolism cage was rinsed with water to give a final volume of 25 ml diluted urine. A blood sample was then taken under ether anaesthesia from the vena cava, and then the left kidney, heart, and brain were removed and weighed. The concentration of lithium in serum and tissue samples was determined by atomic mass absorption spectrophotometry. The concentration of creatinine in serum and urine was determined by the alkaline picrate method.

RESULTS

Table 1 shows the results. The creatinine clearance and the urine flow were significantly reduced in the rats given lithium orotate compared to those in each of the three other groups ($P < 0.001$). Urine flow was significantly higher in rats given lithium carbonate than in the sham treated group ($P < 0.05$). The kidneys weighed significantly more in rats given lithium orotate than in those in the three other groups ($P < 0.001$). Inspection of the kidneys showed those from rats given lithium orotate to be larger and paler than the kidneys from the other rats. The renal lithium clearance was significantly lower ($P < 0.001$) and the lithium concentrations in serum, kidney and heart were significantly higher ($P < 0.001$, 0.005 and 0.01, respectively) 6 h after the injection in rats given lithium orotate than in rats given lithium carbonate.

Table 1. Kidney function and lithium concentrations in rats given an i.p. injection (2 mmol kg^{-1}) 2 h before a 3 h renal clearance test. Values are means (with s.d.) for 6 rats per group. The serum and tissue samples were taken 6 h after the injection.

Treatment	Creatinine clearance ml min^{-1} kg^{-1}	Urine flow rate µl min^{-1} kg^{-1}	Kidney weight g kg^{-1}	Renal lithium clearance ml min^{-1} kg^{-1}	Lithium concentration: Serum mmol l^{-1}	Kidney mmol kg^{-1}	Heart mmol kg^{-1}	Brain mmol kg^{-1}
Lithium orotate	0.22^{abc} (0.20)	12.2^{abc} (10.2)	5.11^{abc} (0.50)	0.05^{a} (0.06)	1.44^{a} (0.19)	2.37^{a} (0.31)	1.96^{a} (0.44)	0.72 (0.21)
Lithium carbonate	6.53 (0.90)	59.5^{c} (19.7)	3.29 (0.27)	1.19 (0.21)	1.00 (0.10)	1.71 (0.18)	1.28 (0.15)	0.60 (0.16)
Sodium chloride	7.32 (1.11)	50.3 (7.5)	3.10 (0.16)					
Sham	7.43 (0.79)	43.7 (8.3)	3.08 (0.29)					

a, *b* and *c* indicate significant differences from the corresponding values in the groups given lithium carbonate, sodium chloride and sham treatment, respectively. See Results for significance levels.

The renal lithium clearance was significantly lower ($P < 0.001$) and the lithium concentrations in serum, kidney and heart were significantly higher ($P < 0.001$, 0.005 and 0.01, respectively) 6 h after the injection in rats given lithium orotate than in rats given lithium carbonate.

DISCUSSION

Kling et al (1978) offered three explanations to account for their findings. One was that since the orotate was injected as a slurry whereas the carbonate was injected as a clear fluid, the solid orotate might act as a slow release dosage form. According to the second explanation the orotate anion might cause metabolic changes which could influence serum lithium values, for example through affecting lithium binding nucleotides. The third explanation was that orotate might influence factors reducing the glomerular filtration rate.

The present findings show that the third explanation of Kling et al was correct. Treatment with lithium orotate in the dosage and manner that they used leads to a marked reduction of the glomerular filtration rate. The creatinine clearance was 25–35 times lower in the rats given lithium orotate than in those given lithium carbonate, sodium chloride or sham treatment. As a result, the renal clearance of lithium was lower and the concentration of lithium in serum and tissues was higher in rats given lithium orotate than in those given lithium carbonate.

We do not know the mechanisms by which lithium orotate treatment reduced the glomerular filtration rate. In our previous study of lithium orotate (Smith 1976) there was no evidence of lowered kidney function in the orotate treated rats, but doses were much lower than in the present experiment. Perhaps high doses of orotate exert toxic actions on the kidney. The intraperitoneal injection of solid lithium orotate (as a slurry) may also have affected kidney function adversely.

Lithium orotate does not appear to offer pharmacokinetic advantages over other lithium salts. Since the orotate anion may exert toxic action on the kidneys, it seems inadvisable to use lithium orotate for the treatment of patients.

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