Lithium Articles

by Hans A. Nieper, M.D.

*Liver Orotate-The Curative Effect of a Combination of Calcium-Orotate and Liver-Orotate on Primary and Secondary Chronic (Aggressive) Hepatitis and Secondary Liver Cirrhosis

From a Lecture held before the International Academy of Preventive Medicine by Hans A. Nieper, Dept. of Medicine, Silbersee Hospital, Hannover

*The Clinical Applications of Lithium Orotate A Two Years Study

*Lithium Orotate, Carbonate and Chloride: Pharmaconkinetics, Polydipsia and Polyuria in Rats

*Lithium Orotate-Excerpt from Dr. Hans A. Nieper's Revolution in Technology Medicine and Society book

LIVER OROTATE

The Curative Effect of a Combination of Calcium-Orotate and Liver-Orotate on Primary and Secondary Chronic (Aggressive) Hepatitis and Primary and Secondary Liver Cirrhosis.

From a Lecture held before the International Academy of Preventive Medicine by Hans A. Nieper, Dept. of Medicine, Silbersee Hospital, Hannover

In previous reports I had repeatedly drawn attention to the effect of Calcium-orotate on osteoporosis, osteochondrosis and malignant decalcification processes, as well as upon chronic immune diseases of mesenchymal tissue and the mucus membrane of the colon. Lithium-orotate was also presented in a publication as being extraordinarily effective at a low dosage in the treatment of endogenous depression, alcoholism, juvenile epileptiform diseases, and above all, genuine migraine. The high complex constants of the orotates enable the mineral to be carried in a bound state through the exterior cell membrane and to be released first, in the process of their metabolism at the plane of the mitochondria, microsomes and lysosomes. (1-5)

In the course of the clinical application of Calcium-orotate (5 years) and Lithium-orotate (2 years) we have carried out a large number of liver biopsies - the checking of eventual side-effects on the liver not being the main reason for the biopsies, yet as a rule of quite considerable secondary interest.

Thereby there not only proved to be complete absence of side-effects of the said orotic-acid salts on the liver, but in the case of Calcium-orotate there was also a good effect, and the combination of Lithium-orotate with Calcium-orotate - a truly striking curative effect on practically all chronic inflammatory processes of the liver, having their origin in the liver mesenchyme.

Magnesium-orotate does not have this effect and neither could the same be proved true after oriented examination for other orotic complexes, a certain exception being orotylcholinate, to which Platt incidentally has already ascribed a sealing effect on the lysosomes of the liver mesenchyme. It is quite proven that in his research Platt found that chronic hepatitis is very essentially sustained by means of a pathological secreting of lysosomal enzymes.(6-7)

In this connection it is important to remember that in practically all forms of chronic hepatitis and cirrhosis of the liver, antimitochondrial, antimicrosomal and antilysosmal anti-bodies (AMA) are to be found, which are being more and more regarded today as the pathogenic principle of the said chronic inflammatory liver diseases (Deborah Doniach). Recently the induction of AMA after a short-term virus hepatitis was proved, as on the whole the induction of AMA and anti-nuclear anti-bodies in the liver can be the consequence of a persistent virus infection. (8)

From differential pharmacodynamic considerations and on the basis of our knowledge which we have of the transport mechanism of the orotates, we can probably explain the healing effect of Calcium-orotate and Lithium-orotate in the following way:

A calcium-ion is set free from the Calcium-orotate at the level of the mitochondrial membranes, which may be effective as a long-term protector against constant immune aggression by AMA. From the lithium-orotate, on the other hand, a lithium-ion is released at the level of the mitochondrial membranes and likewise with great probability at that of the lysosomal membranes, which deplaces Na, thereby dehydrating and stabilizing the lysosomal membranes. Detailed experimental research will be published elsewhere in the future. In any case, after a dose of 150-300 mg Li-orotate daily, a drastic drop of increased SGOT, SGPT and alkaline phosphate can be observed while the gamma GT lags behind in its fall. Li-acetate seems to posses this effect only to a far less extent. Nevertheless at this stage it must be noted that the true curative effect of spring waters on the liver is very essentially due to their Lithium concentration (Henniez, Vichy). According to Loisy, Arnaud, de Grossuvre and Amelot, the lithium level doubles during a course of treatment in Vichy. The detailed works of these authors should be specially drawn to the attention of interested readers at this point. (9)

The treatment of liver patients with Calcium-orotate in combination with Lithium-orotate has still another very fundamental advantage in as much as Calcium-orotate can compensate the side-effects of a long-term cortisone therapy. This is effected in particular by means of an improvement of the calcium fixation in the bones and the avoidance of a negative calcium balance, and furthermore by the protection of the cartilaginous system and prevention of a defective calcium transit at the heart muscle. In the case of three of the following mentioned patients, this protection from cortisone side-effects by means of Calcium-orotate was evidently of great importance for the overall clinical result. We discovered in addition that persistence of the adynamia of the liver patient, which occasionally causes the latter to despair, is not caused by a failure of the above said therapy, but by an especially large decrease of phosphorus as found in whole-blood analysis. This is probably connected with the calcium binding effect of Calcium-orotate in the bone system, whereby the phosphate-pool (patient on liver diet!!) is heavily burdened. Calcium-orotate activates the excretion of insoluble mitochondrial deposit calcium to a great degree (Rasmussen), whereby the bone-building and thus the phosphate consumption is also activated. (10)

> The whole-blood tests are carried out for us by the firm R. Bayer, Stuttgart. 'Recresal' liquid is suitable fir phosphate subsitution. It is well tolerated and its effect on the adynamia is, for the above mentioned reason, always spectacular.

It should be added that the orotates preferentially enter the cells of the mesenchymal tissue. This is most fortunate in consideration of the continually overlooked fact that chronic aggressive hepatitis and cirrhosis are fundamentally diseases of the liver mesenchyme and not primarily of the parenchyma.

Altogether 14 patients were treated exclusively with Calcium-orotate (without Lithium-orotate). 10 of the patients had chronic aggressive hepatitis (five cases post icteric). Of these, 10 patients had an absolute infaust form of development which could not be averted even with cortisone therapy, Azathiprine, Iphosphamide, Silymarine, different applications of treatment and special therapies in liver-hospitals.

Of the patients with cirrhosis, three had a coarse nodular development with oesophagus-varices, two of them with ascites. In one case there was a shrinking biliary cirrhosis of the liver.

After a period of treatment of a least two years with 3g Calcium-orotate daily, all 14 patients are now free of progressive liver disease. Ascites and oesophagus varices are no longer detectable. In four of the cases with chronic aggressive hepatities, it was necessary to carry out a further cortisone therapy at a decreased dosage. Three patients complained of persistent adynamia, distinguised by a very low phosphorus level in the whole-blood. Therapy with 'Recresal' (phosphate) relieved the symptom. The optimum of therapeutic effect was reached after a period of between 9 and 18 months, not earlier.

With the combination of Calcium-orotate with Lithium-orotate the same good clinical results were reached within a much shorter time, as a rule after 2-3 months. This could be demonstrated in 6 cases with aggressive chronic hepatitis and 3 with cirrhosis, one of them of coarse nodular. To these are added 2 patients with chronic hepatitis and cirrhotic development with haemosiderosis, on of them chronic icteric. As a rule the treatment is effective with 2g Calcium-orotate and 150mg Lithium-orotate daily. Only in two cases with chronic post-infectious hepatitis was an extended low-dosed treatment with cortisone necessary for the normalization of the transaminase values.

Remarkably, the histological evidence from the biopsies in the cases with nodular cirrhosis indicates no substantial aspects of improvement, lymphocytic infiltration being above all just as intense as before. This is so, even when a drastic clinical improvement is observed, with vanishing of ascites, normalization of transaminase, ammonium and mineral and phophate balance and the disappearance of malaise.

On the other hand, in the case of 3 out of 3 patients with siderosis, the symptoms of iron-storage have, under the above therapy, totally disappeared, likewise the hyperbilirubinemia.

Judging from the criterium of the SGOT, SGPT, gamma GT and alkaline phosphatase, therapy with Ca-orotate and Li-orotate has very little effect on fatty liver just as cortisones have no effect here. Even the combination of Calcium-Lithium orotate with cortisone does not bring about any improvement.

Summary

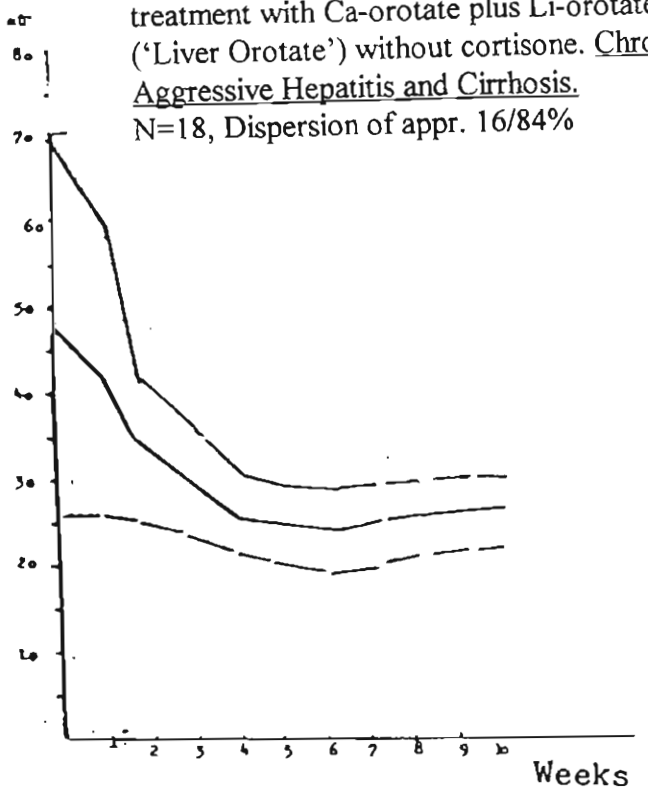
The combination of Calcium-orotate and Lithium-orotate is highly effective in the long-term treatment of chronic aggressive hepatitis and liver cirrhosis. In the treatment of fatty liver the effect is negligible. In serious cases the combination with cortisone therapy

produces exceptionally good results, which are to be achieved neither with Ca-orotate and Li-orotate alone, nor with cortisone alone. Moreover, Calcium-orotate prevents the typical side-effects of cortisone therapy. The effective principle of Calcium-orotate presumably lies in the releasing of Ca-ions at the plane of the mitrochondrial membranes, whereby the aggression of antimitochondrial antibodies may be inhibited. Lithium-orotate releases Li-ions at the lysosomal membranes, so that sodium is withdrawn from them, which is probably equivalent to a lysosomal stabilization. In the leucocyte-model lithium-orotate is a very effective inhibitor of the release of lysosomal enzymes. Platt considers the lysosomal enzymes as being fundamental instigators of chronic hepatitis.

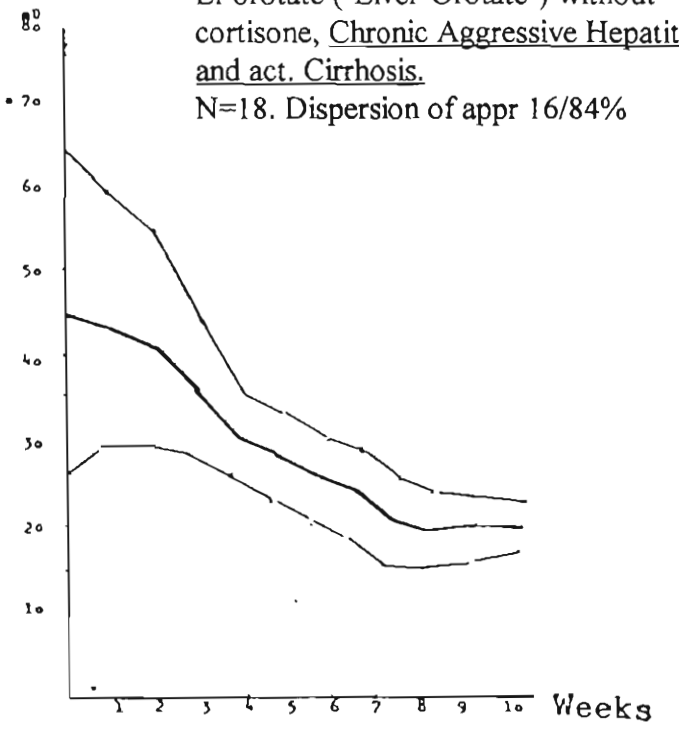
Other orotic-acid salts do not have the above mentioned effect, just as liver therapy with Ca-orotate and Li-orotate has only very little connection with the conventional orotate therapy. The orotic-acid component in the here set-out therapy concept is regarded as the trans-membrane transporter for calcium and lithium into the cells of the liver mesenchyme. In order to avoid adynamy in spite of a good therapeutic effect, a normaliztion of phosphorus in the whole-blood analysis is indicated.

Dr. Hans A. Nieper
21, Sedanstrasse
3000 Hannover

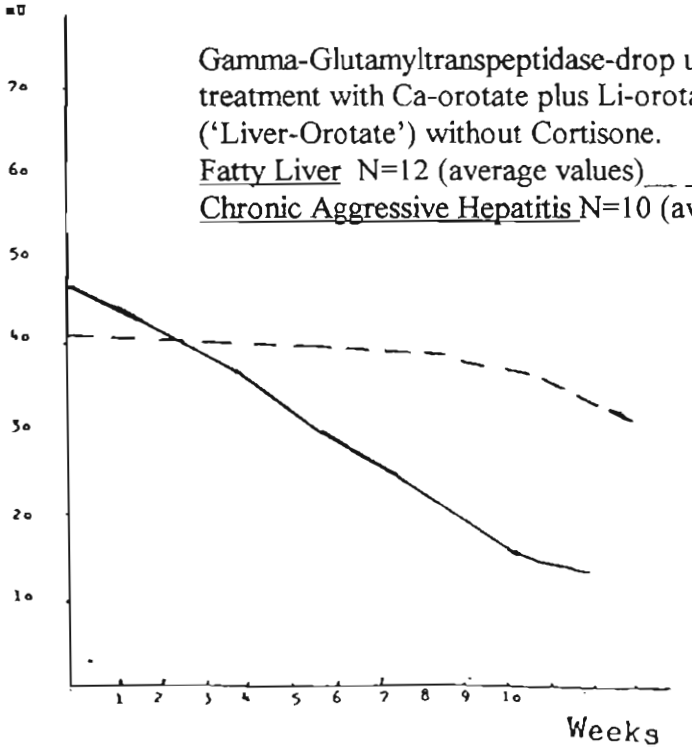
Transaminase drop (SGOT) under treatment with Ca-orotate plus Li-orotate ('Liver Orotate') without cortisone. Chronic Aggressive Hepatitis and Cirrhosis.
N=18, Dispersion of appr. 16/84%



Transaminase drop (SGPT) under treatment with Ca-orotate plus Li-orotate ('Liver-Orotate') without cortisone, Chronic Aggressive Hepatitis and act. Cirrhosis.
N=18. Dispersion of appr 16/84%



Gamma-Glutamyltranspeptidase-drop under treatment with Ca-orotate plus Li-orotate ('Liver-Orotate') without Cortisone.
Fatty Liver N=12 (average values)
Chronic Aggressive Hepatitis N=10 (average values)



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10) Rasmussen, H. Triangel 12,3, 103-109 (1974)
(Triangle)

Additional comments on Lithium Orotate by Dr. Hans A. 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.

Travail reçu le
28 novembre 1973

The Clinical Applications of Lithium Orotate. A Two Years Study

by

H. A. NIEPER

Silbersee Clinic, Hannover-Langenhagen

THE CLINICAL APPLICATIONS OF LITHIUM OROTATE. A TWO YEARS STUDY

H.-A. NIEPER

Agressologie 1973, **14**, 6 : 407-411

Sixty-four patients were treated with lithium orotate and observed for time periods ranging from four months to two and one half years. Lithium orotate is of truly unparalleled efficiency in the treatment of constitutional migraine, constant headache and hemicrania. Also in the treatment of depression, alcoholism and epilepsy, lithium orotate has proven very useful without any problems in the application. Lithium orotate is effective at uncommonly low dosages and causes no negative side effects. Lithium citrate and lithium carbonate are far less effective than lithium orotate.

The specific principle is considered to be a directed intracellular transport of lithium by means of the orotic carrier molecule, which has a high affinity for tissue dependent on the pentose pathway, e.g. glia and the blood brain barrier. The directed carrier principle of the lithium orotate therapy makes a determination of the lithium level in blood serum unnecessary. The effectiveness of lithium therapy as such is based on a membranal and cellular displacement of sodium.

In the autumn of 1969, HAMILTON reported on the dessication of malignant pleura effusions with the help of lithium succinate, given orally in capsules in daily doses of 600 mg. Lithium carbonate and lithium acetate did not possess this therapeutic capacity. We personally followed the progress of one of HAMILTON'S patients and can confirm his observations. We used lithium succinate from the Verdun Company in Montreal for this purpose.

The succinates have an especially great affinity for lipid structures, which may explain the superiority of lithium succinate over lithium carbonate and lithium acetate. The desiccation of malignant pleura effusions can only be explained as the result of a displacement of sodium by lithium in the cells or membranes. The displacement of sodium by lithium is also the working principle behind the lithium therapy in neurology and psychiatry and is due to the progressive scaling of the atomic radii of these substances.

In the past few years, the use of lithium to control depression, constitutional migraine, constant headaches, hemicrania, alcoholism and hyperthyreosis (GERDES 1972) has played an increasingly important role. This led us to examine the applicability of the principle of directed mineral or electrolyte transport to the lithium therapy. Our observations on tissue cultures have established that the orotates such as calcium orotate and magnesium orotate pass through the cell membrane in undissociated form and release their respective ions only at the site of membranes of cytoplasmic structures. It is assumed that this is also true for lithium orotate (NIEPER, 1969, 1970), (fig. 1).

In addition to this phenomenon, the orotates show a special affinity for tissues in which the metabolism involves the pentose pathway, e.g. the glia, vascular walls and especially the blood brain barrier (NIEPER, 1973).

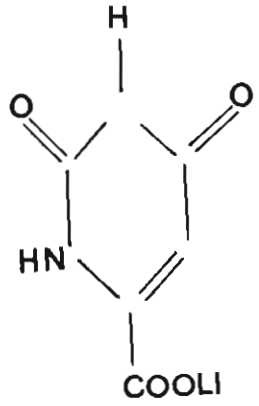

FIGURE 1. — Lithium orotate.

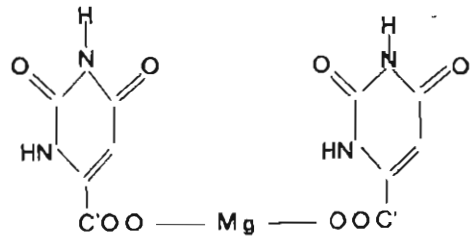

FIGURE 2. — Magnesium orotate

Continuous use of drinking water rich in lithium (El Paso) has been correlated with a low of psychoses (DAWSON, MC GANITY and MOORE, 1972) ; the protective effect of hard water with respect to arteriosclerosis is presumed to be due to the high lithium content. Based on our present knowledge of the course of arteriosclerotic damage, it is probable that the lithium is stabilizing the lysosomal membranes and thus preventing lysosomal damage to the vascular walls, perhaps even to the cardiac muscle itself (VOORS, 1971 . PLATT, 1972). An exactly opposite situation is observed when the level of intracellular sodium is high. The lithium ion of lithium orotate is specifically released in the immediate vicinity of the lysosomes.

We have had lithium orotate in clinical use for two and one half years, treating mainly ambulatory patients. The therapeutic effectiveness has been so spectacular that an extensive report on our work is now in order.

We used stomach acid resistant gelatine capsules filled with 150 mg lithium orotate each. During the long-term therapy, an extremely exact Bausch and Lomb spectromat was used to perform numerous mineral analyses of the patients' whole blood and blood serum. Therapy with lithium orotate does not cause the approximate level of 0.02 ppm lithium in normal whole blood or serum to be exceeded by more than 30 %. It is significant that a completely effective lithium therapy can be achieved without raising the level of lithium in the blood excessively. This also supports the assumption that the lithium orotate molecules transport lithium ions directly into the cell. The removal of reservations related to the toxicity simplifies the lithium therapy in general, especially in the treatment of migraine. At normal doses, a continuous control of the level of lithium in the blood is no longer necessary.

In only three cases did we observe mild symptoms of muscular adynamy, lack of appetite and general listlessness after six to eight weeks of continuous treatment with lithium orotate. These symptoms disappeared when sodium glutamate (bouillon preparation) was given.

The therapy was continued for a minimum of eight weeks with all patients and was reinstated at the reoccurrence of complaints, generally at the lower doses previously achieved. We observed a complete absence of negative side effects with the use of lithium orotate, especially with respect to cardiac and hepatic symptoms. According to capillarographic criteria, the elder patients even showed an increase in blood vessel elasticity during this therapy.

The onset of treatment is usually accompanied by a rapid excretion of water from the body. Myoptic and hyperoptic patients experience a change in vision due to a slight dehydration of the eyes. On the other hand, flicker scotome and other sensations which usually accompany attacks of migraine disappear.

The identity of lithium concentrations in whole blood and blood serum indicates that this substance is normally not the object of a directed transport across membranes. This is why it is especially important to provide lithium with a suitable carrier mechanism. The widely used acetate, carbonate and citrate compounds hardly fulfill this requirement, the succinate and asparaginate do so partially, but the orotate is by far the most effective lithium carrier molecule for the reasons previously discussed in this paper.

We have treated a total of 64 patients with lithium orotate, observing all but 3 of them for more

than four months. The 3 patients who discontinued the therapy prematurely were all alcoholics.

Among the patients were 44 who could be grouped together according to their symptoms of constant headache, migraine and hemicrania. The youngest was fifteen, the oldest seventy-four years old. There were 31 females and 13 males in this group. All of them were dissatisfied with the results achieved by previous treatment. Some complained that the previous therapy had merely lessened the severity of the attacks without preventing them altogether, others claimed that the various treatments were totally ineffective, some were opposed to the use of suppositories and some had experienced unpleasant side effects.

Our analysis of the case histories led us to the discovery that the use of ergotamine preparations, with and without caffeine, yield especially unsatisfactory results. Compounds containing Vitamin B 15 are considered to be helpful in some cases. The most effective compound used to treat constitutional migraine before the introduction of lithium orotate for this purpose is undoubtedly benzoic acid sulfinide (saccharin), which most probably achieves a displacement of sodium similar to the lithium orotate. This compound is, however, virtually unknown in Germany and is no longer applicable.

16 of the 44 patients had previously used analgesic compounds containing lithium citrate (13 patients) or lithium carbonate (3 patients) without therapeutic effect.

Therapy with lithium orotate was started at doses of five to six 150 mg capsules per week. Of the 44 patients, 39 reported the therapy to be thoroughly effective and their use of additional analgesic compounds was drastically limited. The supplementary intake of caffeine was frequently of value. There was virtually no improvement in the conditions of 5 patients, all most probably suffering from occipital pain of cervical or neuroradicular origin.

I cannot recall any medication which was able to achieve such remarkable results in so short a time as does lithium orotate. I have reason to believe that a number of the patients, skeptical of the low dosage, were taking lithium orotate capsules more frequently than necessary. This is, however, completely harmless in every respect.

12 patients were given lithium orotate to control depressive moods or larval endogenic depressions, generally a maximum of five 150 mg capsules per week. 9 patients in all reported an improved condition, of which 3, who also showed an accompanying hyperthyreosis and tendency towards migraine, noted an exceptional betterment.

Of the 8 alcoholics treated with lithium orotate, 3 discontinued the therapy of their own accord after a short time. 2 of them have remained without relapse for more than fifteen months now, especially remarkable since they had each undergone two previous hospitalized withdrawal treatments without success. One had suffered from migraine and both of them suffered from depressions. A comparable case has been under observation for only seven months thus far, but appears to be following the same favorable course. The wives of the remaining 2 patients report that the situation has improved vastly ; their husbands are far less explosive and no longer resort to violence, and they are in general more reasonable than before.

We realize that the number of cases presented here is small, but believe that it is sufficient to compare favorably with the excellent results of KLINE'S double-blind study (1973), as reported by the U.S. Veterans Administration. KLINE achieved a reasonable curative effect in more than half of over 70 sporadic alcoholics with the use of conventional lithium salts. The therapy with lithium orotate appears to be entirely as effective, with the advantage that it is significantly less problematical.

Six patients having manifestations of epileptic disease were also treated with lithium orotate. Four of them, 3 males and 1 female between fourteen and twenty-one years of age, had had an average of one or two convulsive episodes per month. Lithium orotate, given over a period of five to seven months, entirely eliminated the tendency towards convulsions and also lessened the psychic retardation of the patients considerably. These patients had received no medication other than lithium orotate, with the exception of one who also drank an effervescent preparation of magnesium aspartate. Two patients, 1 male and 1 female of thirty-two and forty-five years of age respectively, who were also being treated Mylipsin (primidone), also showed a marked improvement on the lithium orotate therapy. All 6 patients received 150 mg lithium orotate four times per week. We know from our earlier experiments performed with whole blood analysis that epilepsy is also connected with a sodium retention in neural tissue. I feel that it would be very worthwhile to expose lithium orotate to an extensive clinical trial in the treatment of epilepsy.

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RÉSUMÉ

UTILISATION CLINIQUE D'OROTATE DE LITHIUM. ETUDE SUR DEUX ANNÉES

H.-A. NIEPER

Agressologie 1973, **14**, 6 : 407-411

Soixante-quatre malades ont été traités à l'orotate de lithium et surveillés pendant des périodes de quatre mois à deux ans et demi. L'orotate de lithium révèle une efficacité incomparable dans le traitement des migraines constitutionnelles, des céphalées permanentes et des hémicranies. Il s'est montré très utile aussi dans le traitement des dépressions, de l'alcoolisme et de l'épilepsie sans difficultés d'utilisation. L'orotate de lithium est efficace à des doses inhabituellement basses de lithium et ne présente pas d'effets secondaires gênants. Le citrate et le carbonate de lithium sont nettement moins efficaces que l'orotate.

L'apport intracellulaire direct du lithium par le transporteur orotate à affinité élevée pour les tissus à voie des pentoses dominante (glie et barrière hémato-encéphalique) est considéré comme le principe spécifique de cette activité. Ce principe d'apport intracellulaire dirigé rend la détermination du niveau sanguin de lithium inutile. L'efficacité de ce traitement par l'orotate de lithium dépend d'un déplacement du sodium membranaire et cellulaire.

ZUSAMMENFASSUNG

DIE KLINISCHE ANWENDUNG VON LITHIUM-OROTAT, EINE ZWEIJAHRIGE UNTERSUCHUNG

H.-A. NIEPER

Agressologie 1973, **14**, 6 : 407-411

Vierundsechzig Patienten wurden mit Lithium-Orotat behandelt und über eine Zeit von 4 Monaten bis zu 2 1/2 Jahren beobachtet. Lithium-Orotat ist von einer unvergleichlichen Wirkung in der Behandlung konstitutioneller Migräne, von Dauerkopfschmerzen, und von Hämikranie. Auch in der Behandlung von Depressionen, Alkoholismus, und Epilepsie zeigte sich Lithium-Orotat als sehr nützlich ohne irgendwelche Probleme in der Anwendung. Lithium-Orotat ist in ungewöhnlich geringen Dosen wirksam und erzeugt keine negativen Nebeneffekte. Lithium-Citrat und Lithium-Carbonat sind weit weniger wirksam als Lithium-Orotat.

Das spezifische Wirkprinzip wird in dem gerichteten intrazellulären Transport von Lithium mit Hilfe des orotischen Trägermoleküles gesehen. Dieses hat eine hohe Affinität für Gewebe, das vom Pentose-Pathway abhängig ist, wie beispielsweise Glia und die Blut-Liquor-Schranke. Das gerichtete Trägerprinzip des Lithium-Orotates macht eine Bestimmung vom Lithiumspiegel im Blutserum in der Regel überflüssig. Die Wirkung der Lithiumtherapie als solche beruht auf der membranären und zellulären Deplazierung von Natrium.

RÉSUMEN

La aplicacion clinica del orotato de litio : un estudio de dos anos

H.-A. Nieper

Agressologie 1973, **14**, 6 : 407-411

Sesenta y cuatro pacientes fueron tratados con orotato de litio y observados durante períodos de tiempo comprendidos entre cuatro meses y dos anos y medio. El orotato de litio es de una eficacia sin precedentes en el tratamiento de la jaqueca constitucional, cefalea constante y hemicrania. Asimismo, el orotato de litio ha resultado de mucha utilidad y sin problemas de aplicación en el tratamiento de la depresión, el alcoholismo y la epilepsia. El orotato de litio es eficaz a dosis sorprendentemente bajas y no produce efectos secundarios negativos. El citrato de litio y el carbonato de litio resultan de una eficacia considerablemente menor que el orotato de litio.

El principio específico parece ser el transporte celular directo de litio por un portador orótico.

Клиническое применение оротата лития в течении двух лет

Агрессология , 1973 , 14 : 6 : 407 - 411

64 пациента были лечены оротатом лития в периоде от 4 месяцев до двух с половиной лет . Оротат лития обладает выраженной активностью при лечении конституционной мигрени и упорной головной боли , особенно при болях половины головы . При лечении алкоголизма , депрессии и эпилепсии этот препарат обладает выраженным действием без побочных явлений и в очень малых дозах . Оротат лития обладает более выраженной активностью , чем лимоннокислый и углекислый литий .

Авторы предполагают , что действие этого препарата связано , с внутриклеточным транспортом , в оротат играет роль носителя .

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.)

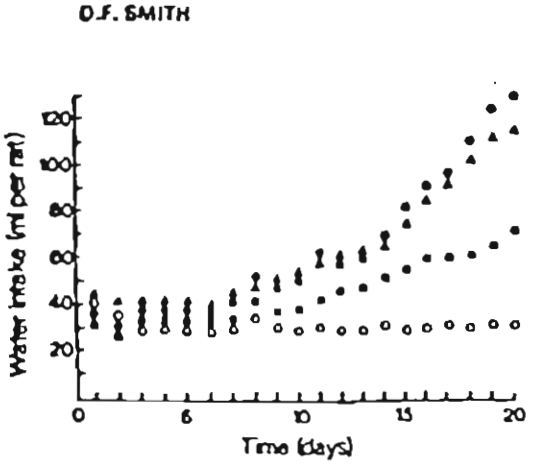
Table 2.

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.

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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.

EXAMPLE: Lithium Orotate

Lithium has proven very useful in the treatment of diseases. Due to its physical characteristics, it displaces sodium in the cellular system. Apparently, its desirable therapeutic effects are related to this fact.

As a rule, orthodox medicine prescribes lithium in the form of its usual salts, such as lithium carbonate. It then becomes necessary to ingest fairly large quantities to achieve the desired effects. These are: improvement in manic and depressive states, improvement in the tendency towards alcoholism, a braking effect on thyroid overproduction and occasionally an improvement in the production of white blood cells, for instance, in the defense against cancerous diseases. Unfortunately, the side effects are not insignificant. These include disturbance of the water balance, fine muscular tremors (fibrillation) and the requirement for fairly frequent lithium blood level controls. As a rule, it may attain 0.6 mval. A trick can be used to overcome these side effects—instead of the usual salts, supply the lithium salt of orotic acid (lithium orotate) which preferentially moves to those cell systems we want to affect, for example, the cells of the connective structure of the brain (the glia cells), the cells of the heart's pacemaker and the heart's stimulus conduction system, and the bone marrow cells. It is thus possible to improve the specific effect of lithium nearly 20 fold. Clinically, 5 mg lithium out of the orotate are approximately as effective as 100 mg lithium out of the carbonate. Examinations of blood serum are no longer necessary because there is no longer any important increase in the serum's lithium content, nor can one be attained. Muscular fibrillation is also prevented, as are disorderly effects on the thyroid. The formation of goiter is avoided, as are undesirable distrubances in the water balance. According to Dr. Kline's studies, in New York, 37% of alcoholics are favorably influenced by lithium carbonate; the figure for lithium orotate would presumably be closer to 70%. In addition, neither the alcoholic nor the emotionally disturbed likes to have to constantly run to the laboratory for lithium controls, as the therapy with the orthodox lithium carbonate requires.

Another lithium compound, the lithium salt of aspartic acid (lithium aspartate), is also considerably more effective than the orthodox carbonate, at a level intermediate between it and lithium orotate.

Even though in 1974 I was elected an honorary member of the Officer's Association of the American Drug Enforcement Police at a large meeting in Anaheim, California (with the corresponding medal), orthodox medicine does still not offer lithium orotate in the treatment of alcoholism, nor in that of mania, nor of light depression or migraine, for which it is also effective.