LITHIUM THERAPY IN PSYCHIATRY WITH SPECIAL EMPHASIS ON BODY WEIGHT

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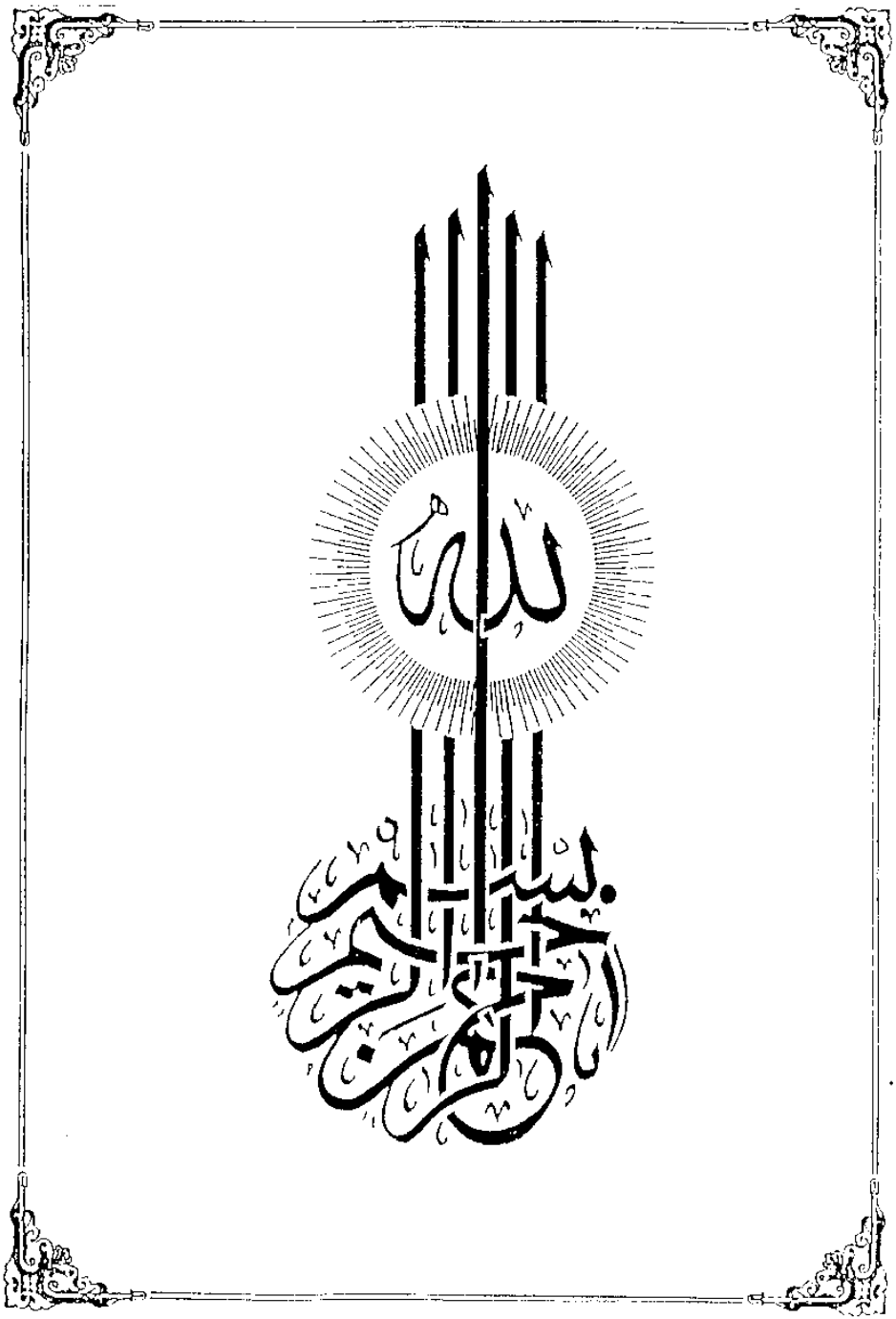

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INTRODUCTION

Lithium, the element, was discovered in 1817 by Arfvedson, within 40 years lithium, the drug, was used in medicine for the treatment of arthritic illness. Throughout the second half of the 19th century, lithium was widely used in patent medicine fashion to treat all forms of aches and pains, achieving a wide (and unjustified) popularity as the vital component of medicinal spring water (Jefferson et al., 1983). At the turn of the century some physicians considered lithium useful in treating melancholia, while others noted its toxicity. It was not, however, until the late 1940s that its therapeutic and toxic potentials were recognized by modern medicine. In 1949, Cade announced his discovery of lithium's remarkable antimanic effect and established it as the first modern psychotherapeutic drug (Cade, 1949). Almost simultaneously, Corcoran et al., (1949) reported severe neurotoxicity and death from the misuse of lithium chloride as a salt substitute. Since 1949, interest in lithium has grown gradually at first but more recently at a steadily increasing rate. By late 1982 more than 9500 medically related lithium articles had been published. Despite lithium's relative maturity as a drug and despite the prodigious amount of work that has been done to understand its actions and apply them to clinical medicine, lithium remains "young" in terms of ongoing basic research, clinical investigation, and applications. So, the aim of this study is to evaluate the role of lithium in psychiatry and throw

some light on its wide range of uses as it is found to be helpful in many psychiatric and non-psychiatric illnesses, and as it becomes more and more prescribed in Egypt the need for knowing more about its side effects, contra-indications and interactions becomes one of the main interest to most of Egyptian psychiatrists.

As a considerable number of Egyptians specially females has a normal tendency to be overweight, and also one of the side effects of lithium is weight gain specially in those who are normally predisposed to. So, the use of lithium could aggravate a problem which is already present in our society, because of that we give special interest to study this topic and to evaluate how could lithium affect body metabolism and endocrinal system to cause weight gain.

GENERAL CONSIDERATIONS

LITHIUM AS A NORMAL TRACE ELEMENT

Lithium is a member of the first group of alkali metals in the periodic table of elements, together with sodium, potassium, rubidium, and cesium (Bowman, et al., 1968). The atomic number of lithium is three, its valency one and atomic weight 6.941. Owing to the peculiar arrangement of the electrons and the high density of the positive change of the nucleus lithium is extremely reactive and the metal never occurs free in nature (Schou, 1978). One of the most interesting physical properties of lithium is an extremely low density of 0.534 g/cm^3 and a boiling point (B.P.) of 1347 ^{o}C. The latter is much higher than those of sodium (889 ^{o}C) and potassium (757 ^{o}C), a fact which should be remembered when choosing flame photometry for lithium determination. In general, the heat of the flame should exceed the boiling point of the metal to be analysed. When lithium salts are heated the lithium ions emits energy in the form of light (red line), the wave length of which is 670.7 nm (Schou, 1978).

Lithium ion has an unusually high hydration energy which accounts for the unusually high solubility of some lithium salts (Hart and Beumel, 1973). This is of importance in the understanding of the kinetics of lithium ions throughout body fluids and across biological membranes. The chloride salt of lithium is an extremely hygroscopic substance, and therefore unsuitable for the incorporation into tablets. For therapeutic purposes, the most widely used is lithium carbonate,

which has a relatively low solubility (1 gm in about 100 ml of water), but more amenable to be dispensed as tablets (Schou, 1968).

Traces of lithium can be detected in many chemical compounds, in more than 150 minerals and in sea and fresh water. It has been found in the tissues of various animals and plants, including tobacco, sugar cane and sea weed (Fieve, 1975).

PHARMACOKINETICS

Lithium is readily absorbed, whether the route of administration is oral, subcutaneous, intramuscular or intraperitoneal (Schou, 1968). However, the only route used in man is oral one, because of the readiness of its absorption by this simple route. Morever, less than 1% of the ingested lithium leaves the body with the faeces which means that more than 99% of the amount ingested is fully absorbed (Hullen et al., 1966). This is more apparent with the citrate and acetate salts more than carbonate (Amdisen and Schou, 1967). It should be noted, however, that different salts contain different amounts of lithium per weight unit, and the lithium content per tablet or capsule varies with the preparation used.

Since lithium is absorbed more quickly than it can be distributed into the tissues, the serum lithium concentrations show steep rise during the first hours after intake. These concentration peaks often

coincides with many of the side effects of the drug. Smoother serum lithium concentration curves with less pronounced variations are obtained when the sustained release (slow - release; retard) form is used. In such preparations the lithium salt is embedded in a matrix that releases lithium gradually. Consequently, there will be fewer and less intense side effects. This also allows less frequent administration, so that even one single daily dose may suffice, and the effects of overdosage could be detected and treated at the proper time (Schou, 1973).

The lithium ion doesn't bind to plasma or tissue proteins, and passes directly from the blood stream into the tissues. Its apparent volume of distribution is about the same as that of total body water. Lithium is not evenly distributed in all tissues; as while its concentration is lower than that in the extracellular fluid, its concentration in muscle, bone, kidney or brain is higher (Davenport, 1950). However, Radomsky (1950) stated that analysis of tissue from animals given lithium for a long time, and from patients who died during lithium treatment have given no indication that lithium is accumulated to considerable amounts in any one organ.

Physiologically speaking, the concentration of lithium in serum is 43.630 n mol/L. The "normal" range of lithium concentration in serum during lithium maintenance therapy is 0.6 - 1.2 n mol/L, while the range is 0.5 - 5 m mol/kg in other body tissue (Schou, 1973). Correlations between the ratio of erythrocyte to plasma lithium (Le/Lp).

and clinical status have been reported by many workers. In many studies this ratio was about 0.5 with a range of 0.44 - 0.65 (Rybokowski et al., 1974; Lee et al., 1975; Warral et al., 1975); but Marini (1977), using sophisticated algebric equations, gave a range of 1.6 - 1.8.

Lithium is filtered freely through the glomerular membrane; but 80% of the filtered load is reabsorbed along with sodium and water in the proximal tubules. The remaining 20% passes onto the distal portions of the nephron, where no, or very little lithium is reabsorbed i.e. almost 20% is excreted in urine. Thus, lithium clearance is about one-fifth of the glomerular filtrate, which equals 0.2 of the "creatinine clearance" (N 100 - 130 ml/min). Accordingly, lithium clearance in adults with normal kidney functions ranges from 15 - 30 ml/min. In any one person, the renal lithium clearance is remarkably constant, and there is little day-to-day variations but it decreases with age. It is important to emphasize here the relation between lithium and sodium excretion, because the balance between these two electrolytes is suggested to be responsible for the therapeutic outcome of the drug (Schou, 1968). Sodium deficiency leads to a compensatory increased reabsorption of lithium from the distal tubules and so less than 20% will be excreted in urine (Smith and Thomson, 1973), i.e. lithium here "acts" as if it is the "doublaire" of sodium (!!). Accordingly, any factor leading to sodium deficiency will lead to increased lithium reabsorption, with a greater risk of toxicity. Factors influencing the sodium level range from those due to low intake in the diet (salt free

diet) or increased excretion by means other than the kidneys e.g. sweat or the concomitant administration of diuretics with saluretic activity as thiazides.

We also have to notice the influence of mania and depression on the pharmacokinetics of lithium. In a longitudinal single-case study of 28 years old woman, had, every month, a premenstrual manic depressive cycle beginning with a hypomanic episode followed by a depression which improved with menstruation. The lithium serum level oscillated in a regular and inverse relationship to the mood changes, although the patient received a constant dosage of lithium : 16.2 m mol/L per day. The lithium level reached its highest value at the time of the greatest intensity of depression (1.10 m mol/L) and its lowest value during the time of hypomania (0.30 m mol/L), whereas it showed only small oscillations around 0.5 m mol/L when the patient's mood was normal. R.B.C. lithium concentration and lithium excretion in the urine followed the same pattern. The daily creatinine excretion was usually within normal limits. It must be hypothesized that there are compartments or stores, to and from which lithium is transported, by mechanisms related to the biological basis of mood changes (Kukopoulos et al., 1985).

MODE OF ACTION

Discussion of lithium's mechanism of action in treating affective disorders is complicated by the lack of known etiologies for affective disorders. Lithium has diverse cellular actions that become manifest as alterations in hormonal, neuronal, and metabolic systems - the same systems that are altered in the course of affective illness, it is not known whether lithium is treating the cause or the symptoms of the disorder. Theories of lithium's actions fall into several distinct categories based on its biologic and biochemical actions: neurotransmission, endocrine system, circadian rhythms and cellular processes.

Neurotransmission :

Lithium interacts with catecholamine, indoleamine, and cholinergic nerve transmission. Many of the effects have been demonstrated in animal studies and have been summarized by Sheard, (1980) and Sugrue, (1981). Acute lithium administration produces an increase in norepinephrine turnover, including increased neuronal uptake of tyrosine, decreased synaptic release, and possibly increased intraneuronal release. Chronic administration produces only slight or nonsignificant changes in norepinephrine turnover.

Results with serotonin (5-HT) are conflicting. Lithium has been shown to have no effect on, to increase, or to decrease 5-HT turnover acutely (first 1 to 5 days) (Show, 1975). Lithium increases tryptophan

uptake and consequent conversion to serotonin, with continued administration, increased tryptophan uptake continues but increased conversion to serotonin does not, and turnover returns to control levels (Show, 1975).

Short-term changes in the synthesis of dopamine have not been observed. With continued administration, however, increased turnover in striatal and mesolimbic brain areas, but not in cerebral cortex or hypothalamus, has been observed. Long-term lithium administration also blocks dopamine-receptor supersensitivity produced by long-term haloperidol administration. Because many of the acute effects are transient, it has been suggested that lithium's therapeutic actions are the result of changes in postsynaptic receptor sensitivity. In addition to preventing dopamine-receptor supersensitivity, lithium decreases beta-adreno receptor-mediated activity and stabilizes opiate receptors (Post et al., 1979).

Endocrine System :

Lithium blocks the release of thyroid hormones and the synthesis of testosterone, Sheard reviewed these actions in discussing lithium's possible antiaggression effect. Lithium blocks the synthesis and release of testosterone, resulting in a compensatory increase in levels of luteinizing hormone (LH). In Sheard's study of lithium's antiaggressive effect in prisoners, he noted increased LH levels but unaltered testosterone levels during lithium administration (Sheard, 1978).