LITHIUM ESTIMATION IN HEALTH AND DISEASES

Essay

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This study gives an account on lithium, a drug used for the treatment of various psychiatric and non-psychiatric conditions. It is sufficient to remark that it stands as one of the most significant landmarks in twentieth - century medicine.

Recent developments in analytical techniques have enabled clinical laboratories to assess lithium levels reliably in variety of biological fluids. It was found that lithium present naturally in the body in extremely minute amounts and, therefore. lithium was considered to be one of the trace elements. However, the function of lithium in the normal state is so far obscure.

There is a definite relationship between serum lithium levels and the nature of the clinical response or of adverse effects and toxic reactions. The development of adequate serum lithium monitoring techniques was important and helpful amongst practicing physicians in the use of lithium therapy.

The present work may shed some light on lithium and its estimation in health and diseases. This study will deal with lithium through the following points of view:

* Physicochemical properties of lithium.
* Pharmacokinetics of lithium.
* The role of lithium in medicine.
* Metabolic and adverse effects of lithium.
* Monitoring lithium levels.

Physicochemical Properties

Physicochemical Properties

- The nature of trace elements.
- Historical background of lithium.
- Chemistry of lithium.
- Chemical and biological relationships.
- Biology of lithium.

PHYSICOCHEMICAL PROPERTIES

THE NATURE OF TRACE ELEMENTS

Many mineral elements occur in living tissues in such small amounts that the early workers were unable to measure their precise concentrations with the analytical methods then available. For this reason they were often mentioned as occurring in "traces" and the term "trace elements" arose to describe them *(Underwood, 1977)*. Trace elements were classified by *Bhagavan (1978)* into three groups:

1. Dietary essentials: believed to be essential for maintenance of normal metabolism such as iron, iodine, copper and zinc.
2. Possibly essentials: on the basis of suggestive but not completely convincing evidence such as bromine, fluorine and barium.
3. Non essentials: such as lithium, rubidium and silicon, which may frequently occur in the blood and soft tissues of the body at level substantially higher than those of most of known essential trace elements.

Essential trace metals have some criteria to fulfill according to *Cotzias (1967) and Mertz (1981)*. They are present in all healthy tissues of all living things, their concentration is fairly constant, their withdrawal from the body induces reproducibly the same structural and physiological abnormalities regardless of the species studies. their addition either prevents or reverse these abnormalities. the abnormalities induced by deficiency are always accompanied by pertinent, specific biochemical changes and these changes vary with different elements, with the degree and duration of dietary deficiency or toxicity and with age and sex. These biochemical changes can be prevented or cured when the deficiency is prevented or cured *(Underwood. 1977).*

The useful metals are mostly capable of easily accepting and delivering extra electrons, which enable them to play a role in catalysing chemical changes *(Crammer. 1983).* They are incorporated into specific nests in protein molecules and nucleic acids, held there by multiple atomic bonds, and the proteins then become enzymes promotic particular metabolic changes: *(Underwood. 1979).* Other useful metals do not have a catlaytic role, but by binding into special zones of protein or nucleotide help to keep the molecules from unfolting or falling apart, and thus control cell permeability and protein synthesis *(Crammer. 1983).* The useless metals have no catalytic activities, but may become toxic in one of two ways, if they are present in sufficient quantities. They may compete with a useful metal for its specific binding nest in the protein, displace it, altering the molecule's enzymatic capacity. Or they may combine with the protein or nucleic acid at quite new points and alter its shape, solubility and biological role *(Spiro. 1980).*

HISTORICAL BACKGROUND OF LITHIUM

lithium as a metal was discovered in 1817 by *Johnson August Arfwedson* in analysing the mineral petalite *(Cade. 1978).* It constitutes about 20 parts per million of igneous rocks of the earth's crust, so it is sparsely but widely distributed, where it leaches into the drinking water and is daily ingested in minute amounts by everyone *(Taylor et al.. 1984).*

Many medicinal properties were ascribed to lithium in the ninteenth century including the amelioration of mental depression. In the 1940, lithium chloride was used as a taste substitute for sodium chloride in patients with cardiovascular disease maintained on a salt-restricted diet. Following several reports of severe side effects; including fatalities, its use was discontinued *(Fieve, 1980).*

About this time *Cade (1949),* in Australia speculated that mania might be caused by an excess of a circulating endogenous toxin related to urea. Believing uric acid to enhance such toxicity, he administered the highly soluble lithium urate salt to guinea pigs. Unexpectedly, lithium protected guinea pigs from urea toxicity and they became tranquilized, as did 10 maniac patients given lithium.

Howeve, it took nearly 20 years for lithium to become established in psychiatric practice by FDA (Food and Drug Administration) of United States Department of Health, Education and Welfare, mainly through the endeavors of Schou in Denmark *(Schou et al., 1981).*

Even now opinions differ as to the usefulness of lithium in psychiatric and medical disorders. As *Kline (1973)* comments "... It seems if we only wait long enough, evryone in the world will try lithium for every thing..."

"CHEMISTRY OF LITHIUM"

Lithium is a metal, the third in the periodic system after hydrogen and helium the first of group I of alkali-metals in periodic table: lithium, sodium, potassium, rubidium and cesium, and it is adjacent to the group II alkaline earth metals, among which magnesium and calcium are biologically important. Lithium has a single electron on the outside orbit of its inert gas core (atom), thereby producing a strong tendency to form a monovalent positive lithium ion which is the only stable form of lithium in the biological system. So, its atomic number is (3), its electronic configuration is (2,1) and its atomic weight is (6.94). Lithium appears to be a silvery white, solid in the metallic state, it can be melted and pured in air without loosing its brightness *(Schou et al., 1981; Mellerup and Jorgensen, 1975)*.

An important aspect of lithium chemistry is the capacity of the element to form organo-lithium compounds usually prescribed as lithium carbonate and lithium citrate *(Lydiard and Gelenberg, 1982)*. As a special chemical properties of lithium, it is relatively inert towards oxygen and halogen. It does not react with oxygen at room temperature but when heated to 100°C or higher it reacts with oxygen yielding lithium oxide and alone it gives the monoxide. Lithium reacts with hydrogen at a red heat (700-800°C) to give lithium hydride which is a colourless crystalline solid, much more stable and less chemically reactive than other alkali metals as sodium hydride *(Hart and Beumel, 1973)*. Lithium also reacts with water, yielding hydrogen and lithium hydroxide which is colourless, soluble in water and gives strongly alkaline solutions. Lithium has least lipid solubility of the alkali metals *(Baldessarini and Lipinski, 1975)*.

The boiling point of lithium is much higher than that of sodium (889°C) and potassium (757°C), being (1350°C), a fact which should be remembered when choosing flame photometry for lithium determination *(Murray, 1984)*.

Table (1): Some properties of Group I and Group II elements

Periodic System group	Name	Symbol	Atomic Number	Atomic Weights	Ions	Ionic radii (A)	Charge density (Coulombs/A^2)*
	Lithium	Li	3	6.94	Li^+	0.60	0.22
I Alkali Metals	Sodium	Na	11	22.99	Na	0.95	0.088
	Potassium	K	19	39.10	K^+	1.33	0.045
	Rubidium	Rb	37	85.47	Rb^+	1.48	0.036
	Cesium	Cs	55	132.91	Cs^+	1.67	0.029
	Beryllium	Be	4	9.01	Be^2	0.31	1.66
II Alkaline	Magnesium	Mg	12	24.31	Mg^{2+}	0.65	0.38
earth metals	Calcium	Ca	20	40.08	Ca^{2+}	0.99	0.16
	Strontium	Sr	38	87.62	Sr^{2+}	1.13	0.12
	Barium	Ba	56	137.34	Ba^{2+}	1.35	0.088
	Radium	Ra	88	226.05	Ra^{3+}	1.43	0.078

* Charge density calculated as: Charge on ion (in Coulombs) divided by 4xx (ionic radius)2. Ionic radius expressed in A

Lithium has small ionic radius, which results in a high charge density, high hydration energy and high oxidation potential. The chemical bonds in various lithium compounds may also be more covalent than the bond in similar alkali compounds *(Hart and Beumel, 1973)*.

CHEMICAL AND BIOLOGICAL RELATIONSHIPS

The ionic radius of lithium is very similar to that of magnesium (0.60 nm and 0.65 nm respectively), and for this reason lithium may compete with magnesium for enzyme sites specifically activated by magnesium. Both bind nitrogen-containing lignade *(Lehn, 1976; Schou et al., 1981)*.

Lithium is characterised by poorly defined coordination number and site geometry like calcium. This may explain why lithium competes effectively for calcium binding sites in systems using carboxyl groups as chelators. The charge density of lithium is most akin to that of calcium, and again one may speculate whether the presence of lithium may mimic an increase in intracellular calcium concentration which is normally extremely low *(Williams, 1976; Marel et al., 1982)*.

Like sodium and potassium, lithium has a single positive ionic charge. Lithium is transported into the cell as efficiently as sodium but it is pumped out of the cell only slowly by the sodium pump. Lithium, unlike other cations, is fairly equally distributed between intra- and extracellular body compartments. This is due to high hydration energy of lithium ion, high solubility of lithium salts. low diffusion coefficient and lipid insolubility of lithium ion *(Schou et al.1981: Rosenthal and Goodwin. 1982).*

BIOLOGY OF LITHIUM

Lithium is found in plants and in animal tissues and fluids. It present naturally in the human body in extremely minute amounts, is raised in therapy *(Crammer. 1983).*

Hamilton et al. (1973) found the mean lithium concentration in normal tissue to be as follows: lymph nodes; 0.13-0.27 $\mu g\ g^{-1}$ wet weight; lung; 0.05-0.07 $\mu g\ g^{-1}$: brain, 3-5 $ng\ g^{-1}$ testis 2-4 $ng\ g^{-1}$ and human blood 4-8 $ng\ g^{-1}$. They estimated the total dietary intake of lithium by an adult to be about 54 - 160 μg per day.

The function of lithium is unknown. No biochemical or physiological system has been found to be lithium dependent, *(Bhagavan. 1978).* Lithium enters into various biochemical activities. enzymes activated by potassium are inhibited by lithium. and the action of calcium and of magnesium are also antagonized. A lithium ion can replace both sodium and potassium in some active transport mechanisms. In vivo as well as in vitro. studies indicate that the passive diffusion of lithium resembles that of sodium *(Lader and Herrington. 1981).* Lithium affects carbohydrate metabolism at several points. namely. hexokinase activity. activation of liver adenyl cyclase and protein kinase. glycogen synthesis and pyruvate kinase activity *(Mellerup and Rafaelsen. 1975).*