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Neuropsychiatric Manifestations of Alkali Metal Deficiency and Excess

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YUNG, C Y *Neuropsychiatric manifestations of alkali metal deficiency and excess* PHARMACOL BIOCHEM BEHAV **21**: Suppl 1, 71–75, 1984 —The alkali metals from the Group IA of the periodic table (lithium, sodium, potassium, rubidium, cesium and francium) are reviewed The neuropsychiatric aspects of alkali metal deficiencies and excesses (intoxications) are described Emphasis was placed on lithium due to its clinical uses The signs and symptoms of these conditions are characterized by features of an organic brain syndrome with dilirium and encephalopathy prevailing. There are no clinically distinctive features that could be reliably used for diagnoses. Sodium and potassium are two essential alkali metals in man. Lithium is used as therapeutic agent in bipolar affective disorders. Rudibium has been investigated for its antidepressant effect in a group of psychiatric disorders. Cesium is under laboratory investigation for its role in carcinogenesis and in depressive illness Very little is known of francium due to its great instability for experimental study

Alkali metals Cesium Lithium Potassium Rubidium Sodium

THE neuropsychiatric syndromes associated with alkali metal deficiency and excess (intoxication) were studied in relationship to their similarities and to differences in their psychiatric manifestations. The alkali metals are univalent metals occupying Group 1A of the periodic table. They are lithium (Li), sodium (Na), potassium (K), rubidium (Rb), cesium (Cs) and francium (Fr). They are electrically positive charged and evolve heat when in contact with water. In the human body, only Na and K are essential and vital to life, so much so that a mere variant in their concentration in either the extracellular or intracellular spaces can produce an acute dysfunction of vital organs as the brain, heart and kidney leading to a life threatening situation.

Clinically, the syndromes of Na and K excess and deficiency are common occurrences in medicine, as in hyponatremia, hypernatremia, hypokalemia and hyperkalemia. These syndromes are invariably secondary to a variety of underlying medical disorders Intoxication occurs either during lithium therapy for affective disorders or from an overdose. There are no reports on lithium deficiency. There is no available data on the neuropsychiatric aspects of Cs, Rb and Fr deficiencies and intoxications, although there are several reports on the treatment of Cs intoxication in man [24, 26, 57]

LITHIUM

Lithium is a monovalent cation, with a number of properties similar to Na and K. It belongs to the same group 1A of the periodic table. Unlike Na^+ and K^+, Li^+ is equally distributed between intracellular and extracellular body compartments. It is transported into the cell as efficiently as Na^+, but it is pumped out slowly via the Na-pump. Lithium possesses a diagonal relationship with other elements, i.e., similar properties with the second and third member of the alkali earth metals, magnesium (Mg) and calcium (Ca). It is also an electrolyte. It has the same electrical charges as Na and K; an ionic radius similar to Mg and charge density similar to Ca. With all these similarities, it is understandable that Li will affect all those systems dependent on or related to Na, K, Mg and Ca. In addition, Li has effect at the cellular and molecular levels, such as enzymes, membrane components and transport mechanisms.

Excess (intoxication) was initially reported in 1913, when it was used as a salt substitute for cardiac disease patients [10,13]. It was not until the wide spread of clinical useage of Li in affective disorders, that Li poisonings with neuropsychiatric deficits have become frequent. Lithium excess may appear either as an acute or as chronic forms of intoxication [8, 11, 33, 64, 65]. For practical purposes, the major signs and symptoms of Li intoxication that is grouped can be summarized into neurological and psychiatric features

The Neurological Features of Li Intoxication

Neurological deficits from Li intoxication may be divided into three categories; (a) the prodromal phase with or without minor neurological signs, (b) acute brain syndrome with encephalitic-like syndrome without permanent deficits [1, 10, 13, 25, 29, 50] and (c), acute brain syndrome with permanent neurological deficits [5, 11, 16, 33, 64, 65].

(a) The prodromal phase The side effects of Li are numerous, affecting almost every body system [8, 17, 35, 59]. It is an accepted clinical practice to regard the presence of tremor, polydipsia, polyuria, restless and irritability as the beginning prodromal signs of possible or impending Li intoxication, until found to be otherwise by serum Li^+ level and no further exacerbation of signs and symptoms [5,58]. One needs to be mindful of the fact that in patients with delirum

due to Li intoxication, there may be a temporal disassociation of serum Li level from the clinical manifestation of Li intoxication [15]

The interesting and preliminary studies by Alexander *et al* [2] on two different forms of Li isotopes is worth mentioning Animals studies showed that there is a striking difference in the toxicity of two forms of isotopes of Li, ^{6}Li and ^{7}Li The ^{6}Li is found to be present in 7 6% of naturally occurring Li, and is more toxic These differences may account for the temporal disassociation of serum Li^{+} from the clinical signs of Li toxicity, as well as for the reports of Li toxicity with low serum Li^{+} concentration Moreover, fine tremor of hands is a common side effect of Li, i e , 44–88% of the patients [27] It may effect the lower jaws and limbs [55] If the tremor is coarse and more flapping, it could be a sign of neurotoxicity [61]. Non-progressive cogwheel rigidity and muscular weakness are also minor neurological signs [21,54]

(b) Acute brain syndrome not due to an intentional or accidental overdose of Li salts can occur abruptly without much warning. The signs are encephalitic-like They are, clouding of the consciousness, hyperpyrexia, intentional tremor, asterixis, repetitious movements or cogwheel rigidity of the extremities, [54] truncal and appendicular ataxia [31], scanning speech, nystagmus and bilateral dysmetria [5], choreoathetosis [48,70], parkinsonism [28], seizures [32], tardive dyskinesia [11], coma and death Most patients recover without residual deficits A case of emergence of myasthenia gravis during Li therapy was reported [45]

(c) Acute brain syndrome with permanent neurological deficits A review of reports on this subject showed that most of the patients reported to be exhibiting neurological deficits due to Li intoxication, were also receiving concomitant medications These medications were, haloperidol (n=7) [11, 16, 59], alcohol abuse with clorazepate [65], superimposed cardiopulmonary complications [33,64], carbamazepine [9], thioridazine [68], phenytoin [23], chlorpromazine [62,64], sulfa methoxazole [65], methyldopa [46] and electroconvulsive therapy [41] Apte reported [5] 2 cases of permanent neurological deficits due to Li toxicity without evidence of other drug use There were a total of 17 cases reported so far of permanent neurological deficits as reviewed most recently by Donaldson [16]. Apte's [5] 2 cases were not included in his report

These clinical presentations of signs and symptoms suggest the involvement of multiple sites in the CNS, i.e , the cerebellum [16,31], the extrapyramidal system as the basal ganglion [70], and the pons [19]. An autopsy finding has been reported in a patient who had permanent neurological deficits three years prior to death [47] The neuropathological findings were extensive damage to the granule and purkinje cells in the cerebellum, gliosis in the dentate nucleus, the inferior olive and the nucleus ruber, cytoplasmic inclusions in various nerve cells of the cranial nerve nuclei, cytoplasmic vacuoles in cells of the supra-optic nucleus. However, little damage could be found in the substantia nigra and in the neostriatum [47]

The Psychiatric Features of Li Intoxication

This involves predominantly the cognitive sphere and functions, occasionally the perceptual system. These changes could range from the very milk and subtle which may escape the attention of both the patient and physician to gross disorganization of mental faculties, such as mental confusion and disorientation The cognitive impairments are characterized by decreased speed of thinking and cognitive processing, slowness in input integration, decreased vigilance, decreased subjective well-being [6] decreased or enhanced creativity in artistic production [51], a relative lowering of the level of memory, poor long-term memory [3, 12, 34, 36, 49, 56] and perceptual processing, impairment in attention, productivity and emotional reactivity [38] A slight but definite impairment of mood, learning, concentration, and memory were found in volunteers receiving Li [7, 30, 43] There are no long-term follow-up studies of patients to determine if these changes are reversible or not There are studies which showed no evidence of cortical dysfunction in patients (n=13) younger than fifty-five years old [20] and Li did not worsen the organic status of mainic depressive patients with concomitant organic brain diseases [69] In addition, Li had no adverse effect on 13 patients tested with "free recall" task [42] However, there were two reports suggesting the increased rate of Li toxicity in patients with schizophrenia (54%) and schizoaffective disorders (71%), although this was not supported by a recent review [68] There may be other factors predisposing patients to Li toxicity, e g , vulnerability of acute psychotic patients, electrolyte deficits marked psychotic symptoms and intensive anxiety

SODIUM (Na)

It is the principle extracellular cation and is continuously being removed from cells by an active energy-requiring transport mechanism The range of plasma sodium value is from 138 to 145 mEq/L, and less then 5 mEq/L in the intracellular fluid

Hyponatremia

A common clinical problem in water and electrolyte balance when Na^{+} level is less than (<136 mEq/L) The neuropsychiatric signs and symptoms varies with the severity and rapidity with which the hyponatremic state develops In chronic hyponatremia, the body may adapt to these slow changes with nonspecific and vague symptoms such as thirst, nausea, abdominal discomfort, a change in sense of taste, nightmares, generalized cramps of hands, fatigue, exhaustion with minimal exertion, apathy, headaches, dulling of mental processes [60] This can be misinterpreted as a depression It can progress to weakness, restlessness, confusion, delirium and coma, muscle twitching, tremor to focal myoclonic or grand mal seizures

The acute onset of hyponatremia presents with features of an organic brain syndrome known as "hyponatremic encephalopathy", such as impaired concentration and recent memory, disorientation, somnolence, coma, illusion and hallcumation Early intervention and treatment can reverse the condition However, prolonged or severe hyponatremia may cause irreversible brain damage and death The pathogenesis is cerebral edema and brainstem herniation

Hypernatremia occurs when the serum concentration is in excess of (>150 mEq/L) The neuropsychiatric symptoms could be mild and subtle if the onset is gradual and with less severe degree of extracellular sodium changes The symptoms are irritability, hyperactivity or lethargy In the acute and severe form, there are changes of personality, stupor, coma and abnormal movements such as tremor, chorea, myoclonic jerks, cogwheel-rigidity, memory impairment and hallucination Other neurological signs are hyperreflexia, seizures, ataxia and EEG changes The pathological findings in the brain are tearing of cerebral blood vessels, multiple

petechial hemorrhage in the cortex or subdural, subaranoid and intracerebral hemorrhages.

Psychiatric Disorders

Hyponatremia may be induced by psychotropic drugs which could set off an inappropriate secretion of antidiuretic hormones Distrubances of sodium balance has been implicated to play a part in affective disorders [6]. At present, there is no evidence to support any of this hypothesis. Judging from the lack of recent publications on this subject in the literature, the role of sodium in affective disorders is being neglected if not ignored.

POTASSIUM (K)

This is the major cation in man and the principle intracellular cation. The normal serum levels vary from 3.5 to 5.5 mEq/L.

Hypokalemia

Psychiatric manifestation of hypokalemia with K^+ levels less than 3 mEq/L is characterized by subtle personality changes such as irritability, apathy, lethargy, psychoneurosis; mood changes as dysphoria, feelings of hopelessness and helplessness and even suicide ideation; and rarely hallucinations. The severe form is presented as an acute brain syndrome with delirium, memory impairment, confusion, and disorientation. There are reports to suggest a decreased K^+ concentration in cerebral tissues of patients who committed suicide [6,66] as well as significant decrease in Na^+ body. Also, K^+ was found low in depressed patients both during the depression and after recovery [53]. A loss of intracellular K^+ and a retention of intracellular Na^+, while the plasma level of both cations remain normal, in both depression and dementia [14].

The neuromuscular symptoms from hypokalemia are paresthesias, cramps; muscle spasms (twitchings pain or tenderness); mild to severe generalized weakness, especially the proximal muscles in the leg and quadriceps; an ascending or flaccid paralysis (if K is <1–2 mEq/L) which can be periodic [52]; and be mistaken as conversion or muscul skeletal disease, respiratory failure and death may ensue if paralysic involves respiratory muscles and the diaphragm Hypokalemia may be due to primary aldosteronism, Cushing's syndrome, non-k-sparing diuretic therapy, laxatives and self-induced vomiting in bulimia, renal tubular acidosis, antibiotic therapy, myeloid and monocytic leukemia, gastrointestinal and renal loss of K, and inflammatory disease.

Hyperkalemia occurs when K^+ plasma levels are greater than 5.5 mEq/L Cerebrocortical functions may remain intact. Neuromuscular symptoms are muscle weakness, dysphasia, dysarthria and ascending or generalized flaccid paralysis (K^+>8 5 mEq/L) Hyperkalemia could be lethal with cardiac asystole and arrest at (10–20 mEq/L). Hyperkalemia can be secondary to renal disease, K-sparing diuretic, tissue breakdown, and excess intravenous K input.

RUBIDIUM

This is found in virtually all biological systems, and resembles potassium physiologically. Laboratory data showed Rb can displace intracellular K^+ mEq for mEq. It has a biological half life of 50 to 60 days. It was used as early as 1877 in cardiac disorder, and 1880 in epilepsy [18]. It has been reported to have a subjective sense of well being with no reports of irreversible side effects The chemical, biochemical, behavioral, clinical properties and the antidepressant effect on mood and behavior of Rb has been extensively reviewed by Fieves [18]. Experimental trials in different patient populations (unipolar and bipolar affective disorders, schizophrenic disorders) of 6 separate clinical trial studies on a total of 130 patients concluded that Rb may exert nuerochemical and behavioral effects opposite to that of Li, i e., it has antidepressant effects with an increase in well being of mood activity Due to its long half-life, its ability to displace K, and lethality to animals when R b enter the blood stream rapidly, require further extensive animal toxicological studies before any extensive clinical trials in human.

CESIUM

This element behaves in the body similar to K^+, i.e., a higher concentration in intracellular than in extracellular compartment. There has been no data available on the effect of Cs^+ on mental functions on humans. There are clinical reports of treatment of accidental exposures to and overdose of Cs with ammonium molybdate and Prussian blue, but there is no description of the psychiatric conditions of these individuals [40]. Animals studies suggest that Cs has stimulant effect on behavior by increasing the responsiveness of rats to environmental features which is opposite of lithium (attenuates stimulus processing). Cs is being used as ^{131}Cs scan for thyroid modules, in positron emission tomography scintillation detectors, and as isotope ^{137}Cs telegamma therapy in largyngeal and skin cancer in Poland [26,57].

FRANCIUM

This is the heaviest member of the alkali family, with an atomic weight of 223 and atomic number of 87. It's chemical property is similar to Cs. Little is known of this metal because of its great instability and its isotope has a short half-cycle.

The foregoing review of literature showed that the clinical manifestations of a mild to moderate degree of alkali metal (Na and K) deficiencies or excesses (Na, K and Li) could mimic a number of psychiatric conditions In hyponatremia, the signs and symptoms are similar to a depressive syndrome. The periodic paralysis in hypokalemia may be mstaken for a conversion hysteria. A hypernatremic state may induce an irritable mood with subtle changes in personality patterns. The severe and acute forms of alkali metal deficiencies or excesses manifest themselves as an organic brain syndrome with deliria which may be difficult to differentiate from an encephalopathy.

The cognitive function impairments due to long term Li use should be alerted in any patient on Li maintenance therapy [8,20]. It appears that there is no distinctive features, clinically, for diagnoses of alkali metal deficiencies and excesses. It remains to rely on a physician's diagnostic acuity and awareness and a laboratory confirmation.

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