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Lithium Adverse Reactions in Psychiatric Patients

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PARAGAS, M G. *Lithium adverse reactions in psychiatric patients* PHARMACOL BIOCHEM BEHAV **21**: Suppl 1, 65–69, 1984 —A brief review of the literature on the adverse reaction of lithium therapy in man is presented This was aimed at both toxic and side effects of lithium on various organ systems of the body. Inconclusive, insufficient or conflicting data were found in several areas of possible lithium-induced toxicity, notably in lithium-associated nephrotoxicity Results of prospective studies are needed to clarify this issue. Adverse reactions derived from continued administration of lithium salts with neuroleptic medications or with electroconvulsive therapy were also reviewed Lithium-induced side effects on the endocrine and gastrointestinal systems were also summarized along with both dermatologic and opthalmologic effects The teratogenicity of lithium during pregnancy and its cardiovascular abnormalities were discussed The target organs of lithium poisoning and their management were also presented

Lithium Organic brain syndrome Nephrotoxicity Neurotoxicity Poisoning

THE tranquilizing effect of lithium (Li) salts was known as far back as the Roman times During the 1800's, Li was used in many ailments, notably for the treatment of gout and other forms of arthritis. It was in 1949, when the Australian Psychiatrist John Cade first made known his historic discovery of lithium's profound antimanic effects in a case report on [7] "Lithium salts in the treatment of psychotic excitement." This coincided with the use of LiCl as a salt substitute in the U.S., which resulted in severe adverse effects including neurotoxicity and even death in some cases. The use of Li then declined. Hence, it was not until 1970 and 1974 when Li salts were approved in the treatment of affective illnesses and for maintenance therapy in manic-depressive illnesses, respectively. In 1975, the American Psychiatric Association, based on the findings of a task force, announced the following. "Lithium is the treatment of first choice in mania if the patients can be managed successfully without additional therapy. ." "Lithium carbonate is effective in preventing or diminishing the intensity of recurrences of bipolar affective illness There is persuasive evidence from controlled studies that it is also effective in unipolar depressive illness."

The clinical use of Li_2CO_3 has increased over the years and the side effects have become more apparent It was the aim of this brief overview to give a synopsis of Li-induced adverse reactions on various body systems

INCIDENCE OF SIDE EFFECTS OF LI THERAPY

In one study there were as many as two thirds of patients with persistent side effects as a consequence of Li treatment [25] and in another study [5] only 18% of the patients studied, who were on long-term Li therapy, were free of side effects. A survey of 237 patients [62,63] showed that 70% of patients complained of increased thirst, (with 25% of these complaining of nocturia), 45% experienced troublesome hand tremor, 20% experienced more than 10 kg weight gain, 20% suffered from diarrhea, 10% had edema and only 10% were free from side effects [63] The most recent survey of Li toxicity in outpatients on maintenance Li therapy was reported by Lyskowski *et al.* [34]. In a longitudinal study of 67 patients 7% were free of all side effects, 63% had only mild complaints, but 30% experienced persistent moderate or severe side effects The most common complaints consisted of thirst, polyuria, dry mouth, tremor, weight changes, restlessness, sleepiness, fatigue and nausea. The incidence of Li side effects increased when Li was coadministered with other psychotropic medications, which confirms Bone *et al.* [5]. The Li-produced adverse reactions were not related to current age, age at onset of illness, severity of illness, or duration of Li therapy The chronicity of Li therapy was not specifically associated with the presence or absence of any of the side effects surveyed

NEPHROTOXICITY

The possibility that long-term Li therapy may cause permanent kidney damage has been investigated by several workers [6, 21, 42]. Available evidence suggests that morphologic renal changes in the form of interstitial fibrosis and focal nephron atrophy are associated with long-term Li treatment [6]. Hestbech *et al* [21] have initially suggested that lithium may cause chronic progressive renal pathology based on the results of renal biopsies in a series of 14 patients who have been treated with Li for 2 to 4 years. Rafaelsen *et al* [42] suggested that pathological evidence of renal damage may occur in 6% to 15% of patients on long-term lithium treatment while others [9,22] found little evidence to prove

that lithium does cause serious renal damage. However, controlled studies are still lacking.

Ramsey and Cox made recommendations on renal assessment of patients prior to Li therapy [43]. These include, (a) a careful medical history and evaluation, with emphasis on a history of illnesses that may affect renal function and of exposure to nephrotoxins, (b) consideration of nephrological consultation if needed, (c) performing of lab test, i.e., UA, BUN and/or serum creatinine and electrolytes, and if possible, creatinine clearance, (d) assessments of serum creatinine levels several times yearly and yearly determination of glomerular filtration rate if possible and (e) patients with marked polyuria (more than 3000 ml/day) should be carefully monitored because of the possible association between kidney damage and renal concentrating defect.

The nephrotoxicity of Li awaits clarification pending results of ongoing prospective studies. Nonetheless, the unproven risk of Li-induced nephrotoxicity must be weighed against the risks of the untreated manic-depressive illness and the consequences of the morbidity and mortality proven for the disease.

NEUROLOGICAL EFFECTS

Neuromuscular Side Effects

A common and troublesome effect of Li is the development of tremor which may persist throughout the duration of therapy. Lithium-induced tremor is a fine rapid tremor, it is an action tremor and is most readily seen under tension. It is made worse by anxiety and in the presence of CNS stimulants like caffeine. Propranolol, but not anticholinergics, has been found to reduce the Li-associated tremor. Other neuromuscular effects of Li are muscular weakness, hyperirritability, twitching and fasciculation A few case reports of myasthenia gravis associated with the Li treatment have been reported [15, 36, 64].

Extrapyramidal Signs [EPS]

Lithium-induced EPS are in the form of rigidity and cogwheeling and at times associated with toxic or near-toxic serum Li^+ levels [1, 13, 53].

Lithium-Induced Seizures

The available data are conflicting regarding the epileptogenic effect of Li in patients with seizure disorders. However, in normal individuals who are on Li, the risk of seizures developing does not seem to be increased. Grand mal seizures and even status epilepticus have been reported in previously healthy individuals with severe Li poisoning [13].

A wide range of neurologic side effects have been reported with Li use, with the more severe symptoms being associated with Li poisoning. Recent reports indicate the appearance of neurotoxicity in patients with therapeutic blood serum Li^+ levels [12, 20, 67]. Some of the symptoms consist of an acute organic brain syndrome which disappeared rapidly after discontinuation of Li therapy [67]. Likewise a 33 year old woman developed neurotoxicity at serum lithium levels between 1.1 and 1.2 mEq/L, whose sensorium cleared within 36 hr following Li discontinuation [12]. In 2 other cases a similar finding was obtained and the recommendation was made by the authors to promptly discontinue Li_2CO^3 in all confusional states regardless of the serum Li^+ concentration [20]. A review of the neurological side effects of Li [13] indicate that these were not infrequent The authors also suggested the classification of neurological side effects into five groups. These consist of: (a) lithium-induced organic brain syndrome, (b) epileptiform seizures, (c) extrapyramidal side-effects, (d) other neurotoxicity (e.g , ataxia, dysarthria) and (e) EEG abnormalities.

Cognitive Effects

In normal subjects, lithium was found to produce: lassitude, lethargy, tension, and cognitive blunting [26]. This was probably due to Li effect on the CNS by slowing the rate of information processing. Memory loss and impaired concentration have been also reported by others [27,29].

Lithium-Induced Organic Brain Syndrome

This syndrome is characterized [20, 52, 67] by the following: (a) symptoms indicating organicity as evidenced by a confusional state with impairment of orientation and other cognitive functions, (b) serum li levels within the therapeutic range, (c) frequently associated with pre-existing or concomitant neurological disorder, (d) disappearance of signs and symptoms of the organic brain syndrome following discontinuation of lithium treatment, (e) elderly patients and schizophrenic patients seem to be more vulnerable to development of this syndrome.

Irreversible Li-induced neurological deficits have been also reported in patients receiving Li therapy [2]. Patients at higher risk are the elderly patients, schizophrenics, patients with pre-existing pathology and patients with pre-existing EEG abnormalities. A recent report [2] described 2 patients who suffered irreversible neurological deficits due to Li intoxication. They found a "fairly consistent combination of neurological findings, deficits in recent memory, limb and truncal ataxia, and choreoathetosis or parkinsonism." They further state that prompt hemodialysis, with 12 to 15 hr sessions as recommended by Von Hartitzsch *et al.* [19], in patients with major neurological deficits with serum Li^+ levels in the toxic range, may prevent or minimize permanent neurological sequelae. Lydiard and Gelenberg [33] in their review state that "no good evidence exists for a cause-effect relationship between properly monitored, long-term Li administration and irreversible CNS damage in patients without preexisting CNS pathology."

NEUROTOXICITY WITH COMBINED USE OF LITHIUM AND NEUROLEPTIC

A neurotoxic encephalopatic syndrome in four patients receiving Li salts and haloperidol were initially reported in 1974 [8]. Thereafter, an increasing number of reports [31, 55, 56] have implicated neurotoxicity with the combined use of Li and neuroleptic drug. This accounts for nine reports reviewed and an additional study of 39 patients who developed neurotoxicity from the Li and neuroleptic combinations. They [4] noted that the neurotoxic reaction was reversible, frequently appeared in the first week of therapy and was characterized by organic psychopathological symptoms, extrapyramidal signs, cerebellar signs and fever However, appropriate doses of Li and haloperidol may be safely administered in combination [3]. An approach to combined administration of Li salts with neuroleptics suggests the initial use of neuroleptics until good control is achieved, and subsequently, Li administration initiated at a low dose, can be added and slowly increased, at which time the neuroleptic may be decreased and eventually discontinued [59].

TOXICITY WITH ELECTROCONVULSIVE TREATMENT COMBINED WITH LITHIUM THERAPY

There have been reports suggesting that this combination may aggravate the adverse effects of both treatments. The data available are inconclusive and no mechanism for this interaction is known. However, since the studies do seem to point out that confusion and delirium may develop, the concurrent use of ECT and Li should be avoided if possible [35,54]

ENDOCRINE EFFECTS

Thyroid Gland

Lithium has been shown to exert inhibitive action on the thyroid gland. This is indicated by (a) inhibition of iodine uptake into the thyroid gland, (b) inhibition of tyrosine iodination, (c) inhibition of tri-iodothy-ronine (T_3) and thyroxine (T_4) release, (d) inhibition of peripheral degradation of thyroid hormone, (e) inhibition of adenyl cyclase, and (f) thyroid-stimulating hormone (TSH) stimulation of the thyroid. The antithyroid effects of Li are evidenced by the fact that 5% of patients treated with Li_2CO_3 developed hypothyroidism and 3% developed benign diffuse non-toxic goiter. Treatment with thyroxine results in disappearance of goiter Hyperthyroidism has been reported in patients treated with Li [45], therefore it has been recommended that baseline thyroid function studies be performed prior to Li therapy (e.g., T_4, thyronine resin uptake T_3RU and TSH). The TSH determinations at 6 month to yearly intervals are recommended as a sensitive and reliable early indicator of decreasing thyroid function

Parathyroid Gland

Lithium-induced hyperparathyroidism has been reported [16] with elevated serum parathyroid hormone and calcium, lowered serum phosphate concentrations, and increased urinary calcium excretion [10].

GASTROINTESTINAL EFFECTS

These symptoms are common side effects of Li therapy but usually appear early in the treatment and may be related to rise in serum Li levels [25]. Ten percent of patients complain of persistent gastrointestinal (GI) side effects, and approximately 20% suffer from mild diarrhea during initiation of Li treatment. GI complaints include: nausea, vomiting, abdominal cramps, anorexia, gastric irritation and epigastric bloating However, it is rare that these adverse effects become severe enough to warrant cessation of Li treatment. There can be some cases of intolerable GI side effects (nausea, vomiting, diarrhea, and abdominal pain) associated with Li_2CO_3 which were promptly relieved in the three patients studied when lithium citrate was substituted

DERMATOLOGIC EFFECTS

Lithium may cause or aggravate dermatological complaints, notably acneiform eruptions and psoriasis. The latter condition may be exacerbated by Li. This may be due to Li inhibitory effect on adenylcyclase which lower further the decreased levels of cyclic AMP in the psoriatic plaques [65]. Dermatological reactions to Li include, (a) maculopapular, acneiform and follicular eruptions, psoriasis and other dermatologic manifestations. Management of skin reactions usually do not require discontinuation of Li salts [11]. Other reports of skin reactions associated with Li therapy include cutaneous ulcers, hyperkeratotic papules, hair loss and drug allergy rashes. A single case report of an adolescent male patient, who received Li_2CO_3 for approximately two weeks and subsequently developed a pruritic maculopapular rash which progressed to exfoliative dermatitis, has raised the issue of potential Li-induced dermatological toxic reaction [30]. Other investigators came to the conclusion that most Li related skin reactions appear to be reversible after Li discontinuation and no evidence is available to suggest the danger of later development of anaphylactic or other potentially lethal effects [11]

OPHTHALMOLOGIC EFFECTS

Infrequently, irritation of the eye is evidenced by tearing and burning may occur during Li-treatment. This may be due to a change in the ionic composition of tears. This condition usually responds to decongestant ophthalmic solutions [37]. Exophthalmos, associated with thyrotoxicosis or independent of it has also been reported [51] and reversible bilateral papilledema has been shown in two patients on long-term Li therapy [39].

OTHER EFFECTS

Weight Gain

There is an approximate 10% to 20% weight gain, i.e., more than 10 kg, in patients receiving Li-treatment and some reports estimated even a higher rate between 20% and 60% of patients gain weight while on Li [40,63]. It is not clear whether weight gain is due to direct effects of Li on an individual mechanism, e.g., polydipsia, fluid retention, insulin-like effect, altered lipid metabolism or thyroid effects or to a combination of factors

Edema of the feet and legs may occur in patients taking lithium. If lithium dosage reduction does not alleviate the edema, cautious and short-term use of diuretics may relieve the edema.

CARDIOVASCULAR EFFECTS

Serious Li-induced cardiotoxicity is infrequent. The most common change in the ECG is T-Wave depression. An estimated 20% of patients show T-Wave changes and these changes have been shown to be benign and reversible [46]. Cardiac sinus node dysfunction was found in patients on Li [17,44] Some of these effects may be related to partial replacement of K^+ by Li^+ intracellularly in the myocardium. Moreover, ventricular arrythmias, atrioventricular block, cardiomyopathy, congestive heart failure with edema have all been reported [17] However, these were quite rare. Also, no increase in S-T depression was determined during exercise stress-testing in persons without a cardiac history [58].

USE OF LITHIUM IN PREGNANCY (TERATOGENICITY)

The International Registry of "Li Babies" (babies born of mothers given Li during the first trimester of pregnancy) have records of 189 cases as of 1977 [50]. Twenty of these babies had malformations, 15 of which involved the heart and great vessels (a significant percentage had Ebstein's anomaly) and 5 malformations involved other organ systems. These data suggest that the fetus may be vulnerable to the development of cardiovascular abnormalities and therefore the use of Li during pregnancy should be avoided especially during the first trimester. Lithium is excreted in breast milk

and the nursing infants' serum Li^+ concentration have been reported to be one-tenth to one-half of the mother's [48,49] Lactating mothers may therefore choose to bottle-feed instead of breast-feeding

LITHIUM POISONING

Lithium intoxication may be caused by accidental or intentional overdose; it may also be caused by the reduction of renal Li clearance and subsequent rise of serum Li levels in the toxic range if dosage of Li is not appropriately reduced. Conditions that may result in reduced renal Li clearance with risk of intoxication are· (a) presence of kidney disease, (b) in the elderly patient with impaired renal functions, (c) sodium deficiency—e.g , dietary salt restriction, (d) extrarenal loss of sodium, (e) dehydration and (f) use of diuretics The first organ systems affected by Li poisoning are the CNS and the kidneys [18,47] and the severity of Li poisoning appears to be proportional to serum Li concentration and duration of exposure to high Li levels [57]. Generalized neurotoxicity appears at levels of 3 0–4 0 mEq/L with the development of seizures, coma, irreversible brain damage and death [60] Death may also follow acute renal failure in lithium poisoning. In a few patients who survive lithium poisoning, permanent neurological sequelae in the form of cerebellar dysfunction have been reported [18,19]

TREATMENT OF LITHIUM POISONING

Acute Overdose

There is no specific antidote for Li overdose Gastric emptying should be done to delay absorption Jensen and Ladefoged [23] reported a case of Li poisoning with prolonged high Li levels in the gastric fluid and this suggests that prolonged nasogastric suction may be indicated Supportive measures should be used as indicated, e g , electrolyte and fluid correction of any deficits Measuring for enhanced Li excretion should be performed, e g., if Na depletion is the cause of reduced renal Li clearance then Na replacement may hasten Li excretion Hemodialysis is the treatment of choice and should be instituted as promptly as possible in all cases of serious Li poisoning [18, 38, 57] Lithium clearance by peritoneal dialysis is about 15 ml/hr, while in hemodialysis the Li clearance is up to 50 ml/hr [18,38]

In conclusion, although adverse and toxic effects have been associated with Li treatment, it remains the specific drug of choice in the treatment of bipolar affective disorder and when appropriately prescribed and monitored, the therapeutic effects of lithium greatly outweigh the risk of its adverse effects It is reassuring to note that a recent epidemiologic study of 800 patients who have received therapy up to 10 years revealed that no progressive increase in mortality was associated with Li-treatment [14]

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