Treatment of the "On-Off" Phenomenon in Parkinsonism with Lithium Carbonate

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Six patients with severe parkinsonism complicated by the "on-off" phenomenon were treated with lithium carbonate in addition to regular antiparkinsonian medications. A randomized double-blind crossover trial of lithium versus placebo was conducted, followed by an open trial of lithium therapy. Five patients had marked reductions in akinesia (mean, 70%) and improved by one grade in Parkinson staging. This result was more striking in male than in female patients, and in all responders benefit has been maintained during the open phase of lithium treatment (mean follow-up of 36 weeks). In no patient was a reduction in akinesia observed during placebo treatment. Lithium carbonate appears to offer a new and potentially effective approach to treatment of the on-off phenomenon.

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The "on-off" phenomenon consists of rapid oscillations between states of relatively normal mobility and akinesia, and is one of the most troublesome problems in the long-term management of patients with Parkinson's syndrome [1, 27, 28, 30]. This phenomenon occurs with increasing frequency after one to three years of L-dopa therapy, earlier when decarboxylase inhibitors are used [28]. It has been estimated that as many as 50% of patients who have been on L-dopa treatment for longer than five years may be affected [27]. Numerous therapies for the on-off phenomenon have been employed, including dietary manipulation [31], peripheral decarboxylase inhibitors [15], dopamine agonists [16, 24, 26], monoamine oxidase B inhibitors [3], and alterations in the dosage and frequency of L-dopa administration [8, 10, 11, 15, 42]. In general, these have achieved only limited success.

The pathophysiology of the on-off phenomenon is not known, although several mechanisms have been proposed [8, 12, 13, 15, 33]. Recent evidence suggests that the on-off phenomenon may be related to fluctuations in the relative sensitivity of striatal dopamine receptors [14, 25]. Postmortem studies of untreated parkinsonian patients have demonstrated increased haloperidol binding and increased dopamine-sensitive adenylate cyclase in the striatum, suggesting dopamine receptor supersensitivity [25, 32]. By contrast, increased binding was not found in parkinsonian patients being chronically treated with L-dopa. Further, in animal studies, high doses of L-dopa can reverse dopamine receptor supersensitivity [14, 17]. It has thus been proposed that chronic L-dopa treatment may "desensitize" dopamine receptors, with resultant loss of dopamine effect [14, 15, 25].

If the on-off phenomenon is related to alterations in striatal dopamine receptor sensitivity, drugs which stabilize these receptors might prove useful in its treatment or prevention. Lithium carbonate is an effective therapy for manic-depressive illness and is thought to act by preventing alterations in catecholamine receptor sensitivity [4, 35, 37]. Pretreatment with lithium carbonate has been shown to prevent dopamine and α- and β-norepinephrine receptor supersensitivity [19, 34, 35]. We recently treated a parkinsonian patient with the on-off phenomenon by adding lithium carbonate to existing antiparkinsonian medications [39]. This resulted in an 80% reduction in the number of hours of "off" activity and has been maintained during eight months of follow-up. Encouraged by this patient's response, we initiated a trial of lithium carbonate and placebo for treatment of the on-off phenomenon.

Patients and Methods

Six patients with severe idiopathic parkinsonism complicated by the on-off phenomenon were studied (Table 1). All had at least stage 3 parkinsonism [21]. No patient had preexisting psychiatric disease or was considered to be depressed on the basis of psychiatric examination and Zung Depression Scale [43]. None had a preexisting medical dis-

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Table 1. Patient Data

Patient No., Age (yr), and Sex	Duration of Parkinsonism (yr)	Duration of "On-Off" Phenomenon	Treatment
1. 55, M	13	2 yr	L-dopa/carbidopa, 10/100 mg 7×/day; bromocriptine, 2.5 mg 8×/day
2. 60, M	5	1 yr	L-dopa/carbidopa, 25/250 mg 4×/day
3. 49, F	15	3 yr	L-dopa/carbidopa, 10/100 mg 7×/day; bromocriptine, 2.5 mg 6×/day
4. 37, F	10	3.5 yr	L-dopa/carbidopa, 25/250 mg 5×/day; bromocriptine, 2.5 mg 10×/day
5. 67, F	3	6 mo	L-dopa/carbidopa, 25/250 mg 4×/day
6. 69, M	13	2 yr	L-dopa/carbidopa, 25/250 mg 3×/day

order, and the electrocardiogram, chest roentgenogram, serum chemistry determinations, hemogram, thyroid panel, and urinalysis were within normal limits.

All patients were receiving L-dopa/carbidopa (Sinemet) in divided doses, and 3 were taking bromocriptine. Each patient was considered by the referring neurologist to be unresponsive to further drug manipulation, and each was on a stable drug dosage at the time of entry into the study. No change in antiparkinsonian medication was made during the course of the study.

Akinesia and dyskinesia were graded hourly during waking hours on a self-assessment form using a quantitative scoring system modified from Fahn [15] (Fig 1). Use of the scale was repeatedly reviewed with the patients to ensure understanding and compliance.

Following the securing of informed consent, patients were entered into a double-blind crossover study of lithium versus placebo. An initial 2-week baseline period was obtained in the patient's home environment. Patients were then randomly assigned to 4 weeks of treatment with lithium carbonate followed by 4 weeks of treatment with an identical-appearing placebo, or the reverse sequence. Thereafter, lithium carbonate was continued in an open study.

The lithium dosage for each patient was determined by a 600 mg test dose using the method of Cooper et al [6, 7]. Serum lithium levels were obtained weekly during both the placebo and the lithium phases of the study. The lithium levels were reviewed weekly by a nonblind collaborator who was responsible for dosage corrections to maintain a therapeutic serum lithium concentration (0.6 to 1.2 mEq/L). Random adjustments in dosage during the placebo phase were made to assure that the study remained blind.

Neurological evaluations were performed weekly throughout the study. Zung Depression Scale was repeated at week 9 to evaluate any change in affect. Hemogram, serum chemistry determinations, thyroid panel, and urinalysis were monitored.

Results

Results are summarized in Table 2. Therapeutic serum levels of lithium carbonate were obtained in all

Fig 1. Daily chart scored by patient for each episode of akinesia ("off") and dyskinesia. Severity is graded on a scale of 0 to 5.

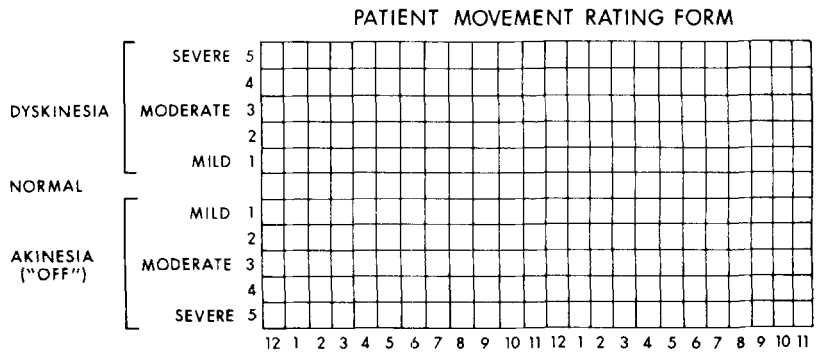


Table 2. Effect of Lithium on Clinical Status

Patient No.	Mean Lithium Level (mEq/L)	% Change in Akinesia[a]	% Change in Dyskinesia[a]	Parkinson Stage[b]		Follow-up[c] (wk)
				Before Lithium	After Lithium	
1	0.85	−75%	+117%	4	3	38
2	0.78	−83%	+89%	4	3	. . .
3	0.65	+24%	0	3	3	18
4	0.80	−62%	−11%	3	2	48
5	0.79	−50%	0	4	3	28
6	0.80	−80%	0	3	2	30

[a]Comparison of mean daily score during baseline with mean daily score during last week of follow-up on lithium.
[b]According to Hoehn and Yahr staging [21].
[c]Weeks of follow-up after completion of double-blind phase of study.

patients. No toxic side effects or changes in laboratory variables occurred in any patient. Five of the 6 patients successfully completed the study. Patient 2 was not able to continue in the study because of injury related to increased mobility during the blind phase of treatment with lithium.

Five of the 6 patients had a marked decrease in "off" activity while taking lithium. This ranged from 50 to 83% (mean, 70%) and was associated with an improvement of one stage in Parkinson grading (see Table 2). In the 3 male patients (Nos. 1, 2, and 6), improvement occurred during the blind phase of the study. In 2 female patients (Nos. 4 and 5), more prolonged treatment was required and improvement was observed only during the open phase of the study. Patient 3 showed no clinical improvement with lithium after an average of 8 weeks of lithium therapy. In no patient was a reduction in akinesia observed during placebo treatment. Benefit has been maintained in all responding patients during the open phase of lithium treatment (mean follow-up of 36 weeks).

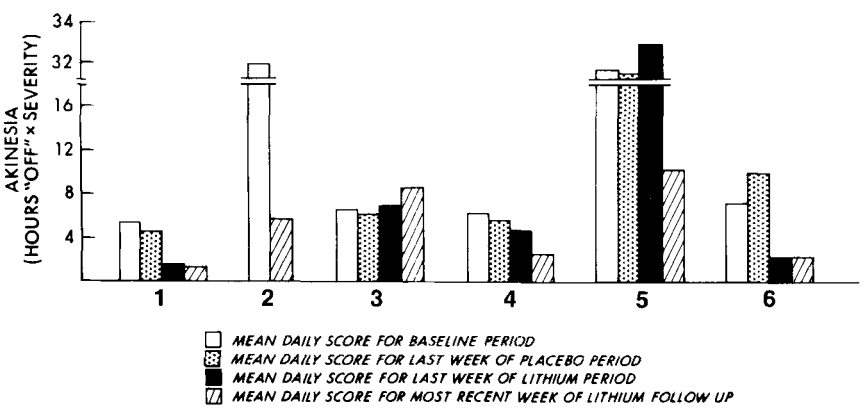
Figure 2 compares the mean daily akinesia ("off") score during the baseline period, during the fourth week of placebo treatment, during the fourth week of "blind" lithium treatment, and during the most recent week of follow-up on lithium. These times were selected because lithium appears to have a latency of 1 to 2 weeks before reaching its maximum effect and a persistent effect for 1 to 2 weeks following its discontinuation [5].

In 2 patients (Nos. 1 and 2) a marked increase in dyskinesia developed in association with the reduction in akinesia during lithium therapy (see Table 2). No significant change in mood was observed in any patient as determined by psychiatric interview and Zung Depression Scale.

Discussion

Only a small body of literature exists on the use of lithium in Parkinson syndrome. Dalen and Steg [9] reported in a letter to *The Lancet* that lithium reduced hyperkinetic involuntary movements in L-dopa–treated parkinsonian patients. Van Woert and Ambani [41] were unable to replicate these findings. McCaul and Stern [29] treated 16 patients with lithium without a significant effect on their parkinso-

Fig 2. Comparison of mean daily akinesia ("off") score obtained for each patient by the method described in Figure 1 for the baseline period, during the last week of placebo, during the last week of "blind" lithium therapy, and during the last week of follow-up with lithium in the open trial.



nian symptoms. Interestingly, however, one of their patients developed "dramatic on-off episodes for the first time" when switched from lithium to placebo.

These reports are difficult to evaluate because of the paucity of clinical data provided on each patient and differences in lithium dosage, serum concentration, duration of treatment, and method of evaluation. It is also not clear whether any of these patients suffered from on-off episodes. By contrast, we observed a marked reduction in akinesia in 5 of our 6 patients with on-off phenomena.

One can only speculate about lithium's method of action. The reduced akinesia, coupled with increased dyskinesia observed in 2 patients, suggests an enhanced dopamine effect. This effect is unlikely to result from increased dopamine synthesis or release, as lithium has been shown to inhibit both striatal dopamine synthesis [18] and dopamine-sensitive adenylate cyclase [40]. Lithium may stabilize dopamine receptors and reduce L-dopa–induced desensitization, rendering the receptor more sensitive to available dopamine [5, 14, 15, 17, 19, 25, 32, 34, 39]. No experimental data exist concerning the effect of lithium on subsensitive dopamine receptors, but lithium has been shown to prevent the development of supersensitivity in experimental animals [19, 34, 35]. Lithium has also been shown to prevent the increase in extrajunctional acetylcholine receptors that occurs in denervated muscle [36]. Cholinergic supersensitivity has been demonstrated in the putamen of parkinsonian patients and may contribute to a diminished response to L-dopa [38]. If lithium has a similar effect on striatal cholinergic receptors, this might result in a relatively increased dopamine response.

Although lithium has a mood-stabilizing effect, mood alterations alone did not appear to be responsible for the changes observed in our patients. All were screened for psychiatric disease prior to entry, and the Zung Depression Scale scores did not change during the course of the study. Furthermore, increases in dyskinesia paralleling reductions in akinesia in some patients suggest a pharmacological (dopaminergic) effect.

One must question why the responses were more striking in male than in female patients. Recent behavioral, endocrinological, and neurochemical data in animals suggest that estrogen may act as an endogenous down-regulator of dopamine receptors and reduce the postsynaptic efficacy of dopamine [2, 20, 22, 23]. Therefore, relatively high concentrations of circulating estrogens may delay or prevent an antiakinesia response to lithium in premenopausal female patients, while lower levels of circulating estrogen in postmenopausal women may permit a greater antiakinesia response. Consistent with this hypothesis, the only female nonresponder in our study was premenopausal, and the woman with the best response was postmenopausal. Furthermore, while prominent dyskinesias developed in 2 of the male patients with lithium therapy, such a response was not seen in any of the female patients. In this regard, Bedard et al [2] have reported on the beneficial effect of estrogen in reducing both tardive- and L-dopa–induced dyskinesia.

This report suggests that lithium may be a valuable adjunct in the treatment of the on-off phenomenon in some patients with Parkinson syndrome. Studies with a larger series and including longer placebo and treatment phases will be required to better evaluate the potential role of lithium, particularly in female patients.

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