British Journal of Dermatology 2004; **150:** 966–969. DOI: 10.1111/j.1365-2133.2004.05822.x

Therapeutics

The effect of inositol supplements on the psoriasis of patients taking lithium: a randomized, placebo-controlled trial

S.J.R.ALLAN, G.M.KAVANAGH,* R.M.HERD† AND J.A.SAVIN*

Department of Dermatology, Victoria Hospital, Kirkcaldy, Fife KY2 5AH, U.K.
**Department of Dermatology, The Royal Infirmary, Edinburgh EH3 9YW, U.K.*
†Department of Dermatology, Western Infirmary, Glasgow G11 6NT, U.K.

Accepted for publication 22 September 2003

Summary

Background Lithium carbonate is the most widely used long-term treatment for bipolar affective disorders, but its ability to trigger and exacerbate psoriasis can become a major problem in patients for whom lithium is the only treatment option. Inositol depletion underlies the action of lithium in bipolar affective disorders and there are good theoretical reasons why the use of inositol supplements might be expected to help this group of patients.

Objectives To determine whether inositol supplements improve the psoriasis of patients on lithium therapy.

Methods Fifteen patients with psoriasis, who were taking lithium, took part in a randomized, double-blind, placebo-controlled, crossover clinical trial comparing the effect of inositol supplements with those of a placebo (lactose). Changes in the severity of their psoriasis were measured by Psoriasis Area and Severity Index scores recorded before and after the different courses of treatment. The effect of inositol supplements on the psoriasis of 11 patients who were not taking lithium was evaluated in the same way.

Results The inositol supplements had a significantly beneficial effect on the psoriasis of patients taking lithium. No such effect was detected on the psoriasis of patients not on lithium.

Conclusions The use of inositol supplements is worth considering for patients with intractable psoriasis who need to continue to take lithium for bipolar affective disorders.

Key words: inositol, lithium, psoriasis, randomized controlled trial

Lithium carbonate is the most widely used long-term treatment for bipolar affective disorders. Unfortunately, this treatment can both trigger psoriasis and make existing psoriasis worse.[1,2] These side-effects can become a major problem in patients for whom lithium is the only treatment option.

On theoretical grounds, inositol supplementation might be expected to help psoriasis aggravated by lithium treatment. The idea that inositol depletion underlies the action of lithium in bipolar affective disorders has been supported by recent research.[3] In addition, inositol supplementation has been shown to reduce some of the other unwanted peripheral effects of lithium without diminishing the beneficial central ones.[4] For this reason we decided to study the value of inositol supplements in patients who had psoriasis and who were taking lithium.

Our pilot study had shown that these supplements were well tolerated, had no obvious side-effects, and seemed to help the psoriasis over periods of several months.[5] We have now followed up this earlier work with a double-blind, randomized, placebo-controlled, crossover clinical trial of the effects of inositol on the psoriasis of patients taking lithium. We have also looked at the effect of inositol on a group of patients with psoriasis who were not taking lithium.

Patients and methods

After ethical approval had been obtained for the trial, 15 subjects were recruited from our dermatology

Correspondence: S.J.R.Allan.
E-mail: Lundieallans@aol.com

outpatient clinics and from the Lothian Lithium Register. All had chronic plaque psoriasis, were over 18 years of age, and had been on lithium therapy for a minimum of 6 months. Those requiring systemic treatment for their psoriasis were excluded. A group of 11 individuals with chronic plaque psoriasis, but who were not taking lithium, was also recruited from our dermatology clinics.

Informed consent was obtained and subjects were asked to avoid canned sports energy drinks and inositol-containing health supplements during the trial. All topical treatment for psoriasis was discontinued at least 2 weeks before the trial began and thereafter only simple emollients were used.

Inositol was given at the dose of 6 g daily. The placebo preparation used was lactose, which is virtually indistinguishable by taste or appearance from inositol. The outcome measure used was the Psoriasis Area and Severity Index (PASI) score,[6] the same observer carrying out all the clinical assessments.

At the start of the trial, patients were allocated to the active treatment or placebo groups by the hospital pharmacist using random number tables, and treatments were dispensed in identical packages. The patients and the examining clinician were blinded to the identity of these treatments. The duration of each treatment period was 10 weeks, and this was followed by a 4-week washout period before starting on the other treatment. Subjects were examined at the beginning of each treatment period, after 5 weeks, and at the end of each treatment period, so that their response could be assessed, and their PASI scores recorded. Adverse effects were also noted.

Statistical analysis

The results were analysed using nonparametric methods (Mann–Whitney test). The difference between the PASI scores pre- and post-treatment was used to compare patients treated with inositol with those treated with placebo. The comparison was made for the whole group and for the controls and lithium patients separately.

Results

Fifteen patients (six men and nine women) on lithium took part in the main trial. They were allocated randomly to two groups: one to take inositol first (mean PASI score 3·2, mean daily lithium dose 671 mg), and the other to take the inositol second (mean PASI score 4·8, mean daily lithium dose 875 mg). Their dosages of lithium ranged from 300 to 1200 mg daily. All completed the trial satisfactorily.

Of the 11 control patients, with psoriasis but not on lithium (three men and eight women), who entered the trial, only eight completed it. One stopped treatment after 4 weeks because of nausea; another withdrew with rapidly worsening psoriasis; and the third failed to attend for review.

When the differences in PASI scores were analysed there was a significant difference between the treatment and placebo groups when controls and lithium patients were combined ($P = 0{\cdot}028$). When controls and lithium patients were examined separately there was no difference between treatment and placebo in the control group but there was a highly significant difference among the lithium-treated patients ($P = 0{\cdot}015$).

The median PASI scores of the two groups at the time of recruitment were 4·0 (range 0·5–7·4) for the lithium group and 4·9 (range 1·7–7·8) for the group not on lithium. The changes in PASI score associated with treatment with inositol and placebo are shown in Table 1 and illustrated in Figure 1. The effects of the

Table 1. Median Psoriasis Area and Severity Index (PASI) scores

Patient group	Treatment	Median (range) PASI score pretreatment	Median (range) PASI score post-treatment
Patients on lithium ($n = 15$)	Inositol	4·9 (0·5–12·9)	3·2 (0–8·3)
	Placebo	3·0 (0·4–7·1)	4·9 (0–16·4)
Patients not on lithium ($n = 8$)	Inositol	4·3 (1·7–6·6)	5·0 (1·0–8·8)
	Placebo	4·35 (1·0–7·2)	3·6 (0·4–7·0)

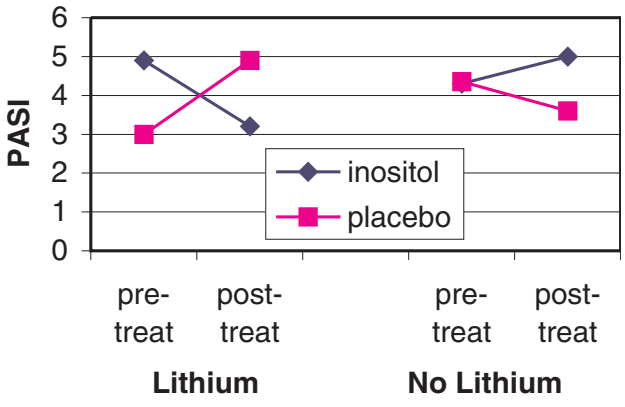

Figure 1. Chart showing median Psoriasis Area and Severity Index (PASI) scores of both groups before and after treatment with inositol and placebo.

Group	Treatment	Improved	Worsened	Unchanged	Did not complete trial
Patients on lithium ($n = 15$)	Inositol	13	2	0	0
	Placebo	7	7	1	0
Patients not on lithium ($n = 11$)	Inositol	5	3	0	3
	Placebo	5	3	0	3

Table 2. The results of treatment as judged by changes in Psoriasis Area and Severity Index score

different treatments on the PASI scores of individual patients are shown in Table 2.

Discussion

Lithium was first used to treat bipolar affective disorders in 1949 and its value had been established by the late 1960s.[7] Since then, despite the introduction of other drugs, lithium has remained the cornerstone of treatment even though it is well known that some patients experience side-effects, usually of a minor nature.[8]

One important side-effect of lithium treatment is its action on psoriasis. This was not detected until 1972,[9] but it is now accepted that lithium therapy can make existing psoriasis worse and even trigger new cases.[1,2] The mechanisms underlying this remain obscure, but may be based on alterations in the metabolism of inositol, a polyhydric alcohol related to monosaccharides, which occurs naturally in animal tissues and in plants.

Inositol is distributed widely in mammalian tissues, existing in its free form, as phosphorylated derivatives and in cell membranes as phosphoinositides. The average human dietary intake of inositol is about 1 g daily and it is freely available without prescription as a nutritional supplement. This is tolerated well, although mild gastrointestinal side-effects such as nausea have been reported.[10] Inositol supplementation has also been used without adverse effects in the treatment of a variety of psychiatric disorders, and of the respiratory distress syndrome in neonates.[11] It seems to be free from specific drug interactions, although high doses of inositol may theoretically have additive effects with selective serotonin reuptake inhibitors.

The 'inositol depletion hypothesis' has been put forward to explain the effect of lithium on manic-depressive psychosis.[12] Inositol is a constituent of the intracellular phosphatidyl inositol second messenger system, which is linked to various neurotransmitter receptors,[13] and brain inositol levels fall as lithium inhibits the action of inositol monophosphatase. Inositol levels in other tissues also fall after lithium treatment.[14] As inositol, if taken in low doses, passes poorly through the blood–brain barrier, treatment with it might be expected to help peripheral side-effects without significantly hindering any beneficial central action. Indeed, inositol has already been used successfully in this way to antagonize some of these peripheral side-effects, such as polyuria,[4] without altering the control of the bipolar affective disorder.[11]

Lithium could affect psoriasis in several ways, one of which may be through the inositol metabolic pathway,[15] and there is some earlier evidence, mainly anecdotal, that patients on lithium with psoriasis have been helped by treatment with oral inositol.[16] The results of our trial confirm this, and suggest also that inositol treatment has no worthwhile effect on the psoriasis of patients who are not taking lithium.

During our study we found no evidence that inositol decreased the efficacy of lithium. There was no obvious worsening of our patients' bipolar affective disorder, although this was not formally assessed. Only one patient required a change in lithium dosage during the trial. It was increased by her psychiatrist early in the trial, but at a time when she was, in fact, on the placebo.

Psoriasis is more common in patients taking lithium than in the general population. In our earlier study,[5] of the 463 patients who completed a postal questionnaire, 10·8% had suffered from it. The use of inositol supplements is worth considering for those whose psoriasis is recalcitrant but who need to continue taking lithium to control their bipolar affective disorder.

Acknowledgment

This study was supported by a grant from the Psoriasis Association.

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