

The Cutaneous Adverse Effects of Lithium

NAVEEN K KANSAL, OMNA CHAWLA, AMANDEEP SINGH, PRITHPAL S MATREJA

ABSTRACT

Lithium is the one of the most commonly prescribed psychotropic medications for bipolar disorder and it is associated with a wide range of cutaneous side effects. Psychiatrists should closely monitor the side effects in patients who are on lithium treatment. Early recognition and proper management

will help in avoiding the issues of noncompliance and the further deterioration of the mood symptoms in these patients. The liaison of psychiatry, dermatology, and primary care services could prove to be very helpful in the management of these patients.

Key Words: Lithium, ipolar disorder, acne, acneiform eruption, psoriasis

INTRODUCTION

Bipolar disorder or manic-depressive illness is a disabling psychiatric illness that is characterized by episodes of both elevated or irritable mood and depression [1]. The manic phase of this life-long, chronic mood disorder is characterized by an elevated, expansive or irritable mood which lasts for at least 1 week (or for any duration if hospitalization is necessary) and is accompanied by at least 3 or more of the following: inflated self esteem/ grandiosity, a decreased need for sleep, pressured speech or over-talkativeness, flight of ideas/ racing thoughts, distractibility and an increase in goal-directed activity/psychomotor agitation, and high-risk behavior; further, the symptoms should not be the direct physiological effect of a substance (e.g. a medication) or a general medical condition (e.g. hyperthyroidism) [2].

Lithium (Gr. lithos, stone) was discovered as an element by Johan August Arfwedson in 1817. About a year later, a Swedish chemist, William Thomas Brande (1788-1866) and an English chemist, Sir Humphry Davy (1778-1829) extracted its pure metallic form [3]. Since Cade's report of lithium use from Australia in 1949, lithium has been the main therapeutic advancement for bipolar disorder [4]. It was approved by the U.S. Food and Drug Administration (FDA) in 1970 for the treatment of acute mania and in 1974 for the maintenance therapy and the prophylaxis of patients with bipolar affective disorder [5]. Lithium, being a monovalent cation (symbol Li⁺), its half-life (t_{1/2}) is about 24 hours and it is excreted unchanged by the kidneys. Lithium has a narrow therapeutic index — a sustained blood lithium level of at least 0.8 mEq/L, with a range of 0.6-1.0 mEq/L should be maintained; [2] the therapy needs to be carefully titrated and monitored. Unlike other psychotropic agents, lithium typically produces no obvious effects (such as euphoria) in normal individuals at therapeutic concentrations, but it acts as a mood stabilizing agent and prevents episodes of mania/ hypomania as well as depression in patients of bipolar disorder. Lithium has also been shown to reduce the risk of suicide [6].

Lithium has a wide range of systemic adverse effects which affect several body systems including the skin [7]. The reported prevalence of the cutaneous side effects varies from 3% to 45% in different

studies. [8,9,10,11,12,13] Acne/acneiform and psoriasiform rashes are among the major cutaneous adverse effects of lithium and these may result in noncompliance; however, not all the patients with pre-existing dermatological disease show flares while they are on lithium treatment. Male patients who take lithium are more susceptible for the development of cutaneous reactions than their female counterparts [8].

MECHANISM OF INDUCTION/ EXACERBATION OF THE SKIN LESIONS

The mechanism by which lithium induces or exacerbates skin diseases is not exactly known, but its role in modulating second messenger systems such as adenylyl cyclase and inositol monophosphatase mediated pathways, resulting in alteration in calcium homeostasis [14]. The decrease in cyclic adenosine monophosphate (cAMP) and inositol that results from lithium treatment causes low intracellular levels of calcium, thus leading to a lack of differentiation and an increased proliferation of keratinocytes and to enhanced chemotaxis and the phagocytic activity of the polymorphonuclear leukocytes. [15] Its effect on the serotonergic function [16] has also been implicated. The pustular propensity of lithium is attributed to lysosomal enzyme release and an increased neutrophil chemotaxis [17,18]. Lithium has been reported to alter the T cell function in vitro [19]. The cutaneous effects of lithium are not related to excessive serum levels of lithium or other evidences of toxicity and may occur at normal therapeutic serum lithium levels [7].

CLINICAL MANIFESTATIONS

The association of psoriasis with lithium was first described by Carter in 1972 [20]. Acneiform eruption due to lithium carbonate was described by Yoder in 1975 [21]; it still remains a prominent cause of drug-induced acne [22]. Other types of skin reactions include acne conglobata, hidradenitis suppurativa, folliculitis, alopecia, thinning of hair, macular/maculopapular rashes, and diffuse, erythematous, pruritic, maculopapular eruption. [23] Other rare cutaneous reactions/ single case reports include lichenoid stomatitis [24], ulcerated lesions of the vaginal mucosa with

acneiform eruption on the thighs [25], follicular hyperkeratosis [26], Darier's disease [27,28], keratoderma [29], oedema, pruritus, urticaria, purpura, allergic vasculitis, pretibial ulceration [30], keratosis pilaris like folliculitis, exfoliative dermatitis, dermatitis herpetiformis like eruption [31], erythema multiforme and linear IgA bullous dermatosis [7].

ACNE AND ACNEIFORM ERUPTIONS

Acneiform eruptions mainly consist of monomorphic pustules on an erythematous base and tend to affect the extremities mainly. These lesions are usually not associated with comedones. Severe conglobata forms and hidradenitis suppurativa might be induced. [32] In a case report, the histological examination of severe acneiform eruption due to lithium on the face, chest and back revealed it to be folliculitis rather than true acne [33]. This type of an eruption may be very resistant to the standard topical dermatological treatment. [32] Psoriasis and psoriasiform lesions.

Lithium has been implicated in a variety of clinico-morphological presentations of psoriasis. The period for the development of psoriasis lesions after the initiation of the lithium treatment is variable and it ranges from a few weeks to several months. Generally, this period is longer for the induction and shorter for the exacerbation of the psoriasis lesions [34]. The common presentation of psoriasis which is secondary to lithium treatment is the typical plaque-type lesions, but other manifestations may also occur and these may include pustular psoriasis [35, 36], scalp psoriasis, fingernail abnormalities [37], erythroderma [38], and psoriatic arthropathy [39, 40]. The histopathological picture of lithium-induced psoriasis is compatible with that of ordinary psoriasis and there are no specific histopathological differences [41].

MANAGEMENT

In evaluating the lithium-treated patients with cutaneous adverse effects, the role of stress and psychological factors, as well as other concomitant medications should be thoroughly evaluated. Acne and acneiform eruptions usually respond to topical antibiotics and retinoids. Psoriasis which is induced or exacerbated by lithium could be managed with conventional treatment methods such as topical steroids, keratolytics, vitamin D analogues, oral retinoids, PUVA (psoralen and ultraviolet A) therapy, and methotrexate. However, many of these side effects may respond less readily to the conventional therapy while the patient is receiving lithium [32]. Reduction in the dose is a reasonable option and it is worth trying. However, in resistant cases, lithium discontinuation may be considered and the patient may be switched on to another mood stabilizer like divalproex. The psoriatic lesions generally disappear within a few months' time after the discontinuation of the lithium treatment. Some newer therapeutic agents which are being used specifically in the treatment of lithium-induced psoriasis include inositol [42], and omega-3 fatty acids [43].

DISCUSSION

Bipolar disorder is a serious mental illness, with most of the patients having a recurrent or chronic illness, thus making it one of the most important causes of disability at the ages from 15–44 years [44]. Lithium is the mainstay of treatment in bipolar disorder, though a number of alternatives are now available like divalproex, other anticonvulsants, atypical antipsychotics like olanzapine, etc. Besides the systemic side effects, lithium is associated with a variety of cutaneous side effects and these may result in suboptimal adherence by the patients. The prescribers should closely monitor

the cutaneous lesions in the patients who are on lithium treatment. Though all the patients with pre-existing skin diseases show flares, skin diseases which are induced and/or exacerbated by lithium treatment may sometimes become difficult to treat with the conventional methods and may manifest as a source of frustration on the part of both the patients and the providers. Therefore, a proper and early recognition and treatment will help in avoiding the issues of noncompliance in therapy and the further deterioration of the mood symptoms in these patients.

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AUTHOR(S):

1. Dr. Naveen K Kansal
2. Dr. Omna Chawla
3. Dr. Amandeep Singh
4. Dr. Prithpal S Matreja

PARTICULARS OF CONTRIBUTORS:

Department of Pharmacology, Gian Sagar Medical College and Hospital, Ramnagar, Patiala, India

NAME, ADDRESS, TELEPHONE, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Amandeep Singh
 Assistant Professor
 Department of Pharmacology
 Gian Sagar Medical College and Hospital
 Ramnagar, Patiala, India
 Phone: + 91-9876102154
 Fax: +91-1762-520024
 Email: angad.aman@gmail.com

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