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Creatine Derivative: Complete Relief of Itch by Topical Administration and Marked Control of Pruritic Dermatitis

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Abstract

Clinical tests and study reveal that the non-toxic creatine derivative, N-acetyl ethyl creatinate topically applied provides rapid and complete relief of itch of various kinds. The compound has been found to be therapeutically effective for eradication or control of various pruritic conditions such as dermatitis and chronic eczema.

Keywords

Dry Skin; Creatine; N-Acetyl Ethyl Creatinate; Chronic Eczema

Introduction

The sensation of itch is expressed only in the skin, in contrast to the sensation of pain which is expressed in all living tissues having functional neurons.

In the skin, itch is transmitted by unmyelinated C-fibers [1]. The cause of itch can be various depending on a presence or absence of erythema or dermatitis. Most commonly itch without dermatitis is due to dry skin, simply relieved by hydration. Otherwise, itch may be the symptom of a more serious dermatologic condition or may be a signal of a disorder of an internal organ or system, e.g. hepatic, renal, neurologic, or of cancer. The present report underscores the importance of our finding a safe and effective topical agent for relief and control of acute or

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chronic eczematous dermatitis. In addition to inflammation, eczema is always associated with itch. Eczema lesions and itch can be improved by topical application of a corticosteroidal cream or ointment such as 0.1% triamcinolone acetonide ointment with or without occlusion. However, there is no cure for eczema in that the lesions of eczema more often persist. One of our research objectives has been to find a cure for eczema.

Creatine, Formula below, taken orally is believed to improve strength, increase lean muscle mass and help the muscles recover more quickly during exercise [2-4]. This muscular boost may help athletes achieve bursts of speed and energy, especially during short bouts of high - intensity activities such as weight lifting or sprinting.



Creatine is an amphoteric compound, both positively and negatively charged in aqueous solution. Therefore, creatine itself cannot readily penetrate human skin and therefore is not bioavailable for therapeutic effects. Certain but different creatine derivatives have been claimed to be useful in the treatment of medical conditions associated with the nervous system [5-8].

Methods

All the creatine derivatives including N-acetyl ethyl creatinate and N-benzoyl ethyl creatinate have been synthesized, purified and identified by mass spectroscopy and HPLC [9].

For topical study, a creatine derivative was usually dissolved in an aqueous solution consisting of water 40 parts, ethanol 40 parts and propylene glycol 20 parts by volume (WEP442) or an anhydrous solution consisting of ethanol 70 parts and propylene glycol 30 parts by volume (EP73).

The creatine derivative, N-acetyl ethyl creatinate (C15) has been used topically against various conditions of itch described in the clinical cases reported herein, in which pruritus was completely relieved by topical application of N-acetyl ethyl creatinate. Formulations were provided to patients/subjects with instructions to apply to sites of itch.

This molecule has been synthesized, purified and identified by mass spectroscopy and HPLC. Same as creatine, N-acetyl ethyl creatinate is a safe compound with LD 50 higher than 400 mg/kg by subcutaneous injection in mice.

Vehicles for topical use of N-acetyl ethyl creatinate (C15) also included:

1. Water: ethanol: propylene glycol 532
2. A lotion made up of hydrophilic ointment USP 35% diluted with 65% water

3. Water: propylene glycol 82

Subjects included ourselves, former patients from dermatologic practice, family members and professional associates. All participants were thoroughly familiar with, or were thoroughly instructed in applicable areas of chemistry, metabolism and in what is generally known regarding inflammation and itch.

Results

We have synthesized various creatine derivatives which are in bioavailable form (Table 1) and found them to be effective in various degree for the relief of itch by topical administration. We have also discovered that the most effective compound is N-acetyl ethyl creatinate which can provide rapid and complete relief of itch and can be therapeutically effective for control of various pruritic conditions and provide sustained relief of chronic eczema.

Compound No.	Compound Name; Anti-itch effect	Structure
C11	Creatinamide 1+	$\text{H}_2\text{NC}(=\text{NH})\text{N}(\text{CH}_3)\text{CH}_2\text{CONH}_2$
C12	ethyl creatinate 2+	$\text{H}_2\text{NC}(=\text{NH})\text{N}(\text{CH}_3)\text{CH}_2\text{COOC}_2\text{H}_5$
C13	N-acetyl creatine 3+	$\text{H}_2\text{NC}(=\text{NAc})\text{N}(\text{CH}_3)\text{CH}_2\text{COOH}$
C15	N-acetyl ethyl creatinate 4+	$\text{H}_2\text{NC}(=\text{NAc})\text{N}(\text{CH}_3)\text{CH}_2\text{COOC}_2\text{H}_5$
C20	N-benzoyl ethyl creatinate 3+	$\text{H}_2\text{NC}(=\text{NBz})\text{N}(\text{CH}_3)\text{CH}_2\text{COOC}_2\text{H}_5$
C26	N-2-acetoxybenzoyl ethyl creatinate 3+	$\text{H}_2\text{NC}(=\text{NAb})\text{N}(\text{CH}_3)\text{CH}_2\text{COOC}_2\text{H}_5$
C27	N-2-acetoxybenzoyl creatine 3+	$\text{H}_2\text{NC}(=\text{NAb})\text{N}(\text{CH}_3)\text{CH}_2\text{COOH}$
C29	N-acetyl propyl creatinate 3+	$\text{H}_2\text{NC}(=\text{NAc})\text{N}(\text{CH}_3)\text{CH}_2\text{COOC}_3\text{H}_7$
C30	N-2-acetoxybenzoyl propyl creatinate 2+	$\text{H}_2\text{NC}(=\text{NAb})\text{N}(\text{CH}_3)\text{CH}_2\text{COOC}_3\text{H}_7$
C31	N-phenylacetyl creatine 2+	$\text{H}_2\text{NC}(=\text{NPc})\text{N}(\text{CH}_3)\text{CH}_2\text{COOH}$
C32	N-phenylacetyl ethyl creatinate 3+	$\text{H}_2\text{NC}(=\text{NPc})\text{N}(\text{CH}_3)\text{CH}_2\text{COOC}_2\text{H}_5$

Table 1: Representative creatine derivatives.

Evaluation of Anti-itch Effectiveness

Five scales were useful to evaluate the efficacy of anti-itch effect: 0 (zero) for no effect; 1+ (25%), which represents partial relief of itch, for less than 6 hours; 2+ (50%), which represents substantial but incomplete relief of itch for less than 6 hours; 3+ (75%), which represents complete relief of itch for less than 6 hours; and 4+ (90-100%), which represents complete relief or eradication of itch for more than 6 hours.

Mosquito Bite Itch Completely Eradicated by Topical N-acetyl ethyl creatinate

Six subjects, 2 males and 4 females' ages 31-74 years who had gathered for a back yard cookout suffered multiple mosquito bites. One subject carried with her 2 ounces of C15 6% in WEP 532 which she shared with the five others for topical application to the pruritic urticarial mosquito bite lesions. All six subjects reported that the itch was completely eradicated within about 1 minute. No itch returned.

Another subject, a 36 year old female, who gave a history of being very sensitive to mosquito bites was provided a solution of C15 6% in WEP 532 to be topically applied to sites of mosquito bite reactions. This solution was later applied to an intensely pruritic urticarial lesion, 1 cm in diameter, due to a mosquito bite. Within 1 minute of application all itch sensation was gone and did not return. Clinical evidence of the lesion began to fade about 3 minutes later and at 5 minutes subject had no sensory awareness of the lesion as it disappeared over the next 10-15 minutes.

A 28 year old female subject applied the same above formulation to mosquito bites. Itch was relieved immediately and signs of the bite disappeared within 1 hour.

Two 9 year old girls and one 9 year old boy applied the same above formulation to mosquito bite sites. Itch was relieved immediately and the physical evidence of the bite disappeared within 1 hour.

Poison Ivy Dermatitis Itch Instantly and Completely Relieved by Topical Application of N-acetyl ethyl creatinate and Dermatitis Resolved within Four Days

A 55 year old male subject developed poison ivy dermatitis of his forearms about 18 hours after pruning bushes. Itch was intense at 24 hours when he applied C15 10% in a lotion made up of hydrophilic ointment USP 35% diluted with 65% water. Relief of itch was immediate, lasting for about 6 hours when C15 was again applied. Duration of itch relief next was for about

10 hours and the next for 12-15 hours. Relief was longer and longer after subsequent applications. Subject reported that signs and symptoms of dermatitis were gone at 4 days.

Relief of Itch and Improvement of Eczema by Topical N-acetyl ethyl creatinate

A 31 year old male, with a 25 year history of eczema, was provided a topical formulation of 6% C15 in a lotion made up of hydrophilic ointment USP 35% diluted with 65% water. After ten days of topical applications itch was relieved for intervals of 1.5 hour up to 24 hours. The patient felt that his eczema was improving almost completely during the summer. At the end of the following February he reported that his eczema was still almost completely gone. Sites of emerging itch were treated with prompt application of the above lotion which completely aborted further development.

A 19 year old female subject with a 14 year history of atopic eczema was provided the same lotion. After 2 weeks of applying the lotion topically, she reported that itch was relieved completely for 24-48 hours following single applications. Patient has moved from the area and has been lost to long term follow up.

A 40 year old female, with a history of eczema for 35 years, was provided the same lotion formulation. After 4 days of application to relieve itch as needed, she reported that itch became negligible. With applications as needed her skin became nearly entirely free of signs of eczema. She expressed great gratitude and hoped that the same beneficial results would persist during the autumn and winter months. At the end of February she reported that her skin had remained clear and "I use it sparingly. If I feel any itch or see a little patch I put it on and it's gone like the next day. When it was hot and cold last week I would put a little on at night just in case and I never had an issue. It's so great. It's miraculous!"

Complete Relief of Itch of Dermatitis of Uncertain Etiology by Topical N-acetyl ethyl creatinate

A 36 year old female subject, who had worked planting a new rock and flower garden during the day, in the evening became acutely aware of an itch sensation in the lower back, just below the beltline. A photo of this area revealed it to be diffusely erythematous with scattered numerous punctate sites more intensely erythematous. Itch was completely relieved by topical applications of C15 4% in water: propylene glycol 8:2 that had been provided to her earlier for possible use on mosquito bites. Itch relief occurred immediately and lasted for 2-3 hours; three additional applications were made during the night. The dermatitis and itch resolved early next day. Etiology was not ascertained.

Burning Itch Induced by *Mucuna Pruriens* Spicules Completely Relieved by Topical N-acetyl ethyl creatinate [10]

Pods containing beans were obtained from Afro Caribe Botanica, 16 separate specimens. In each container innumerable spicules were also present. Small round brushes marketed for interdental cleaning were used to collect spicules.

Applications to sites on both volar and extensor surfaces of a forearm were made by rubbing the skin with such brush with adherent spicules.

7 subjects participated in this study:

1. A 99 year old male
2. A 65 year old male
3. A 77 year old male
4. A 45 year old male
5. A 61 year old female
6. A 60 year old female
7. A 44 year old female

In six subjects burning itch developed within 5-7 minutes. Topical applications of C15 10% in a lotion made up of hydrophilic ointment USP 35% diluted with 65% water, or in water: ethanol: propylene glycol 532 gave complete relief of itch within 2-5 minutes. Relief was permanent.

On the forearm of the 45 year old male there appeared an edematous and erythematous site with only a sensation of mild itch which was relieved completely by C15 topical lotion formulation.

Discussion

The foregoing tests and studies reveal that the creatine derivative N-acetyl ethyl creatinate applied topically completely relieves itch of many kinds. Moreover, in the cases of eczema, not only was itch relieved, but the entire clinical expression of the disease was almost completely eliminated. The rapid action of analgesic effect from topical applications of N-acetyl ethyl creatinate (C15), as we have recently reported, suggests that analgesic effect is mediated through epidermal receptor molecule [9]. We believe the rapid action of anti-itch effect could be mediated through a similar but different receptor molecule in the epidermis. Hypothetically

such receptor molecule(s) most likely would be a large glycoprotein present at the nerve endings in the epidermis.

The fact of a single derivative of creatine completely relieving both pain and itch seems important to comprehending a heretofore unrecognized relationship between these sensory feelings and moreover indicates that this compound has potential immense clinical application.

Design, synthesis and testing of other relevant molecules with greater efficacy could be a goal to strive for.

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Conflict of Interest

The authors declare no conflict of interest.

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