Review

Urea: a comprehensive review of the clinical literature

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Abstract

Introduction: Urea is an organic compound that has been used clinically for dermatological diseases for more than a century. Urea is a potent emollient and keratolytic agent, making urea an effective monotherapy for conditions associated with dry and scaly skin. A systematic review of the literature is needed to provide clinicians with evidence-based applications of urea in the treatment of dermatological diseases.

Methods: A PubMed search was conducted using the term “urea” combined with “skin,” “ichthyosis,” “psoriasis,” “xerosis,” “emollient,” “onychomycosis,” “dermatitis,” and “avulsion.” A total of 81 publications met inclusion criteria and were evaluated. Treatment indication(s), test agents, number of subjects, treatment protocols, results, and side effects were recorded.

Results: Effective treatment with urea has been reported for the following conditions: ichthyosis, xerosis, atopic dermatitis/eczema, contact dermatitis, radiation induced dermatitis, psoriasis/seborrheic dermatitis, onychomycosis, tinea pedis, keratosis, pruritus, and dystrophic nails. Furthermore, urea has been used with other medications as a penetration enhancing agent. Mild irritation is the most common adverse event, proving urea to be a safe and tolerable topical drug without systemic toxicity.

Discussion/Conclusion: Urea is a safe, effective dermatologic therapy with wide-ranging clinical utility and minimal, non-systemic side effects. In order to optimize patient care, dermatologists should be well informed with regards to urea’s indications and efficacy.

Keywords: urea, ichthyosis, xerosis, dermatitis, eczema, psoriasis, onychomycosis, pruritus, tinea pedis, avulsion

Introduction

The efficacy and safety of urea in the treatment of skin diseases has been reported for more than a century. Urea is an organic compound chemically structured as a carbonyl group attached to two amine residues. Physiologically, urea plays an important role in the metabolism and excretion of nitrogen-containing products. Since it was first described, a substantial and evolving literature has been established describing its therapeutic role in the treatment of a myriad of dermatologic conditions. Urea has been employed as a proteolytic agent for wound debridement as well as a topical bacteriostatic agent in wounds [1–4]. As far back as 1957, urea was viewed as an old, forgotten therapy when Kligman wrote, “it sometimes happens in the enthusiastic search for new therapeutic agents that some old stand-by has been overlooked, whose luster has worn off, but which none the less may have some useful application in moments when the miracle drugs falter. In the world of topical therapy, urea is such a drug [5].” We seek to reacquaint the medical community with the versatile clinical applications of urea by conducting a systematic review of the literature and summarizing published findings examining the efficacy of urea in treating dermatological conditions.
Current labeling of urea products includes indications for: (1) debridement and promotion of normal healing of hyperkeratotic surface lesions, particularly where healing is retarded by local infection, necrotic tissue, fibrinous or purulent debris, or eschar; (2) hyperkeratotic conditions such as dry, rough skin, dermatitis, psoriasis, xerosis, ichthyosis, eczema, keratosis, keratosis pilaris, keratosis palmare, keratoderma, corns, and calluses; and (3) damaged, ingrown, and devitalized nails [6–12]. Although the mechanism of action of urea in skin is still unknown, studies suggest that the keratolytic and hydrating effects of topical urea is owing to breakage of hydrogen bonds in the stratum corneum, loosening epidermal keratin, and increasing water-binding sites [13]. Commercially available products containing prescription-grade urea concentrations are listed in Table 1 [6–12].

### Table 1. Common commercially available prescription-grade urea products

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Manufacturer*</th>
<th>Formulation</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carmol 40[6]</td>
<td>Doak Dermatologics</td>
<td>40% urea</td>
<td>Lotion, cream, or gel</td>
</tr>
<tr>
<td>U-Kera E[7]</td>
<td>TaroPharma</td>
<td>40% urea</td>
<td>Emollient cream</td>
</tr>
<tr>
<td>Urealac[8]</td>
<td>Hi-Tech Pharmacal Co.</td>
<td>50% urea</td>
<td>Topical suspension with lactic acid and salicylic acid</td>
</tr>
<tr>
<td>Umecta[9]</td>
<td>Innocutis</td>
<td>40% urea</td>
<td>Emulsion, topical suspension, nail film suspension with applicator, or mousse</td>
</tr>
<tr>
<td>Vanamide[10]</td>
<td>Dermik Laboratories</td>
<td>40% urea</td>
<td>Cream</td>
</tr>
<tr>
<td>RE U40[12]</td>
<td>River’s Edge</td>
<td>40% urea</td>
<td>Foam</td>
</tr>
</tbody>
</table>

*Manufacturer may differ

### Methods

A PubMed search was conducted from inception to December 2011 using the term “urea” combined with “skin,” “ichthyosis,” “psoriasis,” “xerosis,” “emollient,” “onychomycosis,” “dermatitis,” and “avulsion.” The search results were reviewed for clinical trials, case reports, and case series examining the usage and efficacy of urea to treat dermatologic conditions. Additional articles were identified within the citations of qualifying publications that met inclusion criteria but were not returned in the initial PubMed search. The following information was recorded from these publications: the dermatologic condition being studied, test agents, number of subjects, treatment protocol, results, and side-effect profile.

### Results

We obtained and reviewed 284 articles on urea therapies. Of these articles, 81 met our criteria of: 1) being a clinical study, case series or case report, 2) having urea as one of the experimental agents, and 3) describing a dermatological application for urea. The articles were then categorized by treatment for the following conditions: ichthyosis (11 articles), hydration of xerotic/healthy skin (14 articles), atopic dermatitis/eczema (10 articles), contact dermatitis (1 article), radiation-induced dermatitis (1 article), psoriasis/seborrheic dermatitis (14 articles), onychomycosis (5 articles), tinea pedis (4 articles), keratosis (13 articles), pruritus (1 article), dystrophic nails (2 articles), and penetration enhancement (5 articles). For each disease, we provide a summary of the literature highlighting the clinical efficacy and safety of urea treatment and a table detailing clinical trials or case reports for the more studied diseases.
Figure 1. Patient with hyperkeratotic skin before (1A) and after (1B) treatment with 40% urea cream (U-Kera E [7]) for 12 days. Visible clinical improvement in skin texture is observed.

Ichthyosis

Ichthyosis refers to a heterogeneous subset of dermatologic conditions characterized by dry, thickened, and scaly skin. Although the most common form of ichthyosis is ichthyosis vulgaris, a variety of other disorders exhibit ichthyosiform scale. Topical urea has been shown to be an effective therapeutic option for patients with these disorders in a number of studies and expert opinions [14,15]. Urea (10%) was found to be equally or slightly more efficacious in controlling ichthyotic symptoms than 1% hydrocortisone cream [16], 2% salicylic acid ointment, and paraffin-based moisturizers [17]. The beneficial effects of urea on ichthyotic skin can be attributed to its water binding, barrier regenerating, desquamating, and anti-microbial properties [18,19]. Reports of only occasional mild burning or irritation associated with the use of topical urea preparations support an excellent safety profile. The studies are outlined in Table 2 [14–17,20–26].

<table>
<thead>
<tr>
<th>Disease Subtype</th>
<th>Test Agent</th>
<th>Comparison Agent</th>
<th>N</th>
<th>Study Design</th>
<th>Treatment Protocol</th>
<th>Results</th>
<th>Safety (N)*</th>
<th>Year</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bullosa of Siemens</td>
<td>10% urea lotion</td>
<td>5% lactic acid lotion</td>
<td>1</td>
<td>CT BL</td>
<td>BID x 8 weeks</td>
<td>Greater improvements with test agent based on global severity scale</td>
<td>No adverse effects reported</td>
<td>1998</td>
<td>[20]</td>
</tr>
<tr>
<td>Congenital</td>
<td>10% urea cream</td>
<td>Urea-free base cream</td>
<td>2</td>
<td>CT BL</td>
<td>QD x 4 weeks</td>
<td>Test agent produced “soft skin with visible changes like erythema”</td>
<td>No adverse effects reported</td>
<td>1968</td>
<td>[21]</td>
</tr>
<tr>
<td>Epidermolytic hyperkeratosis (EHK)</td>
<td>10% urea</td>
<td>None</td>
<td>1</td>
<td>CS</td>
<td>QD</td>
<td>90% improvement after 6 months</td>
<td>No adverse effects reported</td>
<td>2009</td>
<td>[22]</td>
</tr>
<tr>
<td>Keratitis-ichthyosis-deafness (KID) syndrome</td>
<td>5% and 10% urea cream</td>
<td>None</td>
<td>1</td>
<td>CR</td>
<td>QD x 2 weeks</td>
<td>Marked improvement in hyperkeratosis and palmoplantar keratoderma after 2 weeks of therapy</td>
<td>No adverse effects reported</td>
<td>2007</td>
<td>[23]</td>
</tr>
<tr>
<td>Laevis</td>
<td>10% urea cream</td>
<td>Urea-free base cream</td>
<td>2</td>
<td>CT BL</td>
<td>QD x 4 weeks</td>
<td>Test agent produced “normal appearance of skin”</td>
<td>No adverse effects reported</td>
<td>1968</td>
<td>[21]</td>
</tr>
<tr>
<td>Lamellar</td>
<td>5% urea emulsion</td>
<td>None</td>
<td>5</td>
<td>CS</td>
<td>BID x 6 weeks and 4 month maintenance</td>
<td>Improvement was observed in all treated areas</td>
<td>Mild burning, pruritus and irritation (2)</td>
<td>2011</td>
<td>[15]</td>
</tr>
<tr>
<td>Lamellar</td>
<td>10% urea lotion</td>
<td>5% lactic acid lotion</td>
<td>11</td>
<td>CT BL</td>
<td>BID x 8 weeks</td>
<td>Greater improvements with test agent based on global severity scale</td>
<td>No adverse effects reported</td>
<td>1998</td>
<td>[20]</td>
</tr>
<tr>
<td>Linearis</td>
<td>10% urea cream</td>
<td>Urea-free base cream</td>
<td>1</td>
<td>CT BL</td>
<td>Max 4 weeks</td>
<td>Test agent produced “normal appearance of skin”</td>
<td>No adverse effects reported</td>
<td>1968</td>
<td>[21]</td>
</tr>
<tr>
<td>Unspecified type with history of or present eczema</td>
<td>10% urea cream (pH 6 and 3)</td>
<td>None</td>
<td>30</td>
<td>CT BL</td>
<td>BID x 4 weeks</td>
<td>Both test agents improved skin conditions</td>
<td>Burning sensation (2) with pH</td>
<td>1975</td>
<td>[24]</td>
</tr>
</tbody>
</table>
Numerous randomized controlled trials support the use of urea in the treatment of xerosis. Typically administered in concentrations less than or equal to 10%, the hydrating properties of urea can offer clinical benefit to patients with xerosis [27,28]. In many studies, transepidermal water loss (TEWL) is used as the primary parameter for assessing skin hydration. Several experiments have shown that urea can reduce TEWL in both xerotic and healthy skin [29]. Cream was shown to be a slightly better vehicle than foam in one study [30]. Studies on the hydrating effects of urea in patients with either xerotic or healthy skin are outlined in Table 3[14,16,29,31–33] and Table 4[30,34–40], respectively.

### Table 3. Clinical studies of the hydrating effects of urea in patients with xerosis

<table>
<thead>
<tr>
<th>Test Agent</th>
<th>Comparison Agent</th>
<th>N</th>
<th>Study design</th>
<th>Treatment Protocol</th>
<th>Results</th>
<th>Safety (N)*</th>
<th>Year</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% urea lotion with dexamethasone</td>
<td>None</td>
<td>15*</td>
<td>OL</td>
<td>BID x 4 weeks</td>
<td>Test agent improved skin dryness and pruritus</td>
<td>Mild burning (1)</td>
<td>2011</td>
<td>[31]</td>
</tr>
<tr>
<td>15% urea</td>
<td>Untreated</td>
<td>12</td>
<td>CT BL</td>
<td>BID x 2 weeks</td>
<td>Test agent reduced TEWL in all individuals</td>
<td>No adverse effects reported</td>
<td>2009</td>
<td>[29]</td>
</tr>
</tbody>
</table>
Abbreviations: CT - controlled trial, OL - open label, CS – case series, CR – case report, BL – bilateral comparison (test versus control), QD – once daily, BID – twice daily, TID – thrice daily, TEWL – transepidermal water loss

Table 4. Clinical studies of the hydrating effects of urea in healthy subjects

<table>
<thead>
<tr>
<th>Test Agent</th>
<th>Comparison Agent</th>
<th>N</th>
<th>Study design</th>
<th>Treatment Protocol</th>
<th>Results</th>
<th>Safety (N)*</th>
<th>Year</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-10% urea in cream or foam</td>
<td>Untreated</td>
<td>61</td>
<td>CT BL</td>
<td>3 separate studies conducted, varying protocols</td>
<td>Cream was better than foam in reducing TEWL and improving hydration</td>
<td>No adverse effects reported</td>
<td>2011</td>
<td>[30]</td>
</tr>
<tr>
<td>Urea with vitamins and ceramides</td>
<td>Urea alone</td>
<td>10</td>
<td>CT</td>
<td>QD x 2 weeks</td>
<td>Combination treatment superior in improving hydration and increasing gene expression of transglutaminase-1, loricrin and filaggrin</td>
<td>No adverse effects reported</td>
<td>2008</td>
<td>[34]</td>
</tr>
<tr>
<td>Urea/NaCl emulsion</td>
<td>Urea alone</td>
<td>23</td>
<td>CT BL</td>
<td>BID x two weeks</td>
<td>Both agents equally effective in skin hydration</td>
<td>No adverse effects reported</td>
<td>2002</td>
<td>[35]</td>
</tr>
<tr>
<td>5% urea cream</td>
<td>5% hydrogenated canola oil</td>
<td>13</td>
<td>CT BL</td>
<td>BID x 2 weeks</td>
<td>Test agent decreased TEWL and reduced the irritant effects of sodium lauryl sulfate at day 14</td>
<td>No adverse effects reported</td>
<td>1997</td>
<td>[36]</td>
</tr>
<tr>
<td>10% urea emulsion</td>
<td>Various formulations</td>
<td>72</td>
<td>CT</td>
<td>BID or TID x max 20 days</td>
<td>TEWL and irritation to sodium lauryl sulfate was decreased after pre-treatment with test agent</td>
<td>No adverse effects reported</td>
<td>1996</td>
<td>[37]</td>
</tr>
<tr>
<td>2-4% urea cream</td>
<td>None</td>
<td>6</td>
<td>OL</td>
<td>Moisturizer x 1 hour followed by 0.25 – 24h exposure to SLS irritant</td>
<td>Test agent improves water retention by various parameters that quantified stratum corneum dynamic function</td>
<td>No adverse effects reported</td>
<td>1995</td>
<td>[38]</td>
</tr>
<tr>
<td>10% urea emulsion</td>
<td>Urea-free vehicle</td>
<td>54</td>
<td>CT</td>
<td>Heels treated TID x 3 days</td>
<td>Test agent increased the amount of cutaneous free water in the presence of high relative humidity</td>
<td>No adverse effects reported</td>
<td>1995</td>
<td>[39]</td>
</tr>
<tr>
<td>Moisturizers with varying urea content</td>
<td>Urea-free vehicle</td>
<td>26</td>
<td>CT</td>
<td>Measured epidermal hydration 3 hours after application</td>
<td>Test agent potently humidified skin and removed scale agent</td>
<td>No adverse effects reported</td>
<td>1992</td>
<td>[40]</td>
</tr>
</tbody>
</table>

Abbreviations: CT - controlled trial, OL - open label, CS – case series, CR – case report, BL – bilateral comparison (test versus control), QD – once daily, BID – twice daily, TID – thrice daily, TEWL – transepidermal water loss

Atopic Dermatitis/Eczema

Urea has been shown to improve stratum corneum hydration, water-binding capacity, and TEWL in eczematus skin [41]. The use of urea in atopic dermatitis has been studied most often using a concentration of 10% alone or in combination with 1% hydrocortisone [42]. Combination therapy with betamethasone-17-valerate has also been found to be clinically effective [43]. Nearly all studies demonstrated clinical improvement with urea treatment. Occasional stinging and burning were common side effects. The studies are outlined in Table 5 [21,24,41,43–48].
## Table 5. Clinical studies of urea in patients with atopic dermatitis

<table>
<thead>
<tr>
<th>Test Agent</th>
<th>Comparison Agent</th>
<th>N</th>
<th>Study Design</th>
<th>Treatment Protocol</th>
<th>Results</th>
<th>*Safety (N)</th>
<th>Year</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% urea cream</td>
<td>None</td>
<td>10</td>
<td>OL</td>
<td>Observation performed 2 hours after application</td>
<td>Test agent improved stratum corneum hydration, water-binding capacity, and TEWL</td>
<td>No adverse effects reported</td>
<td>1989</td>
<td>[41]</td>
</tr>
<tr>
<td>10% urea + 1% hydrocortisone</td>
<td>0.1% hydrocortisone-17-butyrate</td>
<td>46</td>
<td>CT</td>
<td>QD x 3 weeks</td>
<td>No statistical difference between agents</td>
<td>No adverse effects reported</td>
<td>1979</td>
<td>[44]</td>
</tr>
<tr>
<td>10% urea cream, pH 6</td>
<td>10% urea cream, pH 3</td>
<td>30**</td>
<td>CT BL</td>
<td>BID x 4 weeks</td>
<td>Test agent showed statistically improved efficacy and acceptability</td>
<td>Burning sensation in more acidic preparation (13)</td>
<td>1975</td>
<td>[24]</td>
</tr>
<tr>
<td>1% hydrocortisone in 10% urea</td>
<td>0.1% betamethasone 17 valerate</td>
<td>36</td>
<td>CT BL</td>
<td>TID x 2-4 weeks</td>
<td>Comparable efficacy in majority of patients for both agents</td>
<td>No adverse effects reported</td>
<td>1974</td>
<td>[45]</td>
</tr>
<tr>
<td>1% hydrocortisone in 10% urea</td>
<td>0.1% betamethasone 17 valerate</td>
<td>49</td>
<td>CT BL</td>
<td>QD x 2 weeks</td>
<td>No statistical difference between two agents</td>
<td>No adverse effects reported</td>
<td>1974</td>
<td>[46]</td>
</tr>
<tr>
<td>1% hydrocortisone in 10% urea</td>
<td>Acidic 1% hydrocortisone in 10% urea</td>
<td>41</td>
<td>CT BL</td>
<td>QD x 2 weeks</td>
<td>Non-acidic test agent was clinically superior to acidic preparation</td>
<td>No adverse effects reported</td>
<td>1974</td>
<td>[46]</td>
</tr>
<tr>
<td>10% urea + 1% hydrocortisone cream</td>
<td>1% hydrocortisone</td>
<td>48</td>
<td>CT BL</td>
<td>TID up to 5 weeks</td>
<td>Test agent was clinically superior to hydrocortisone alone.</td>
<td>Stinging (23)</td>
<td>1973</td>
<td>[47]</td>
</tr>
<tr>
<td>1% hydrocortisone in 10% urea</td>
<td>0.1% betamethasone-17-valerate</td>
<td>50</td>
<td>CT BL</td>
<td>BID x 2-3 weeks</td>
<td>Test agent was less effective than comparison agent.</td>
<td>Excoriated skin (6)</td>
<td>1973</td>
<td>[48]</td>
</tr>
<tr>
<td>10% urea + 0.1% betamethasone-17-valerate</td>
<td>0.1% betamethasone-17-valerate alone</td>
<td>42</td>
<td>CT BL</td>
<td>QD x 10 days</td>
<td>Test agent showed greater improvement with normal skin restored in 18 patients</td>
<td>No adverse effects reported</td>
<td>1971</td>
<td>[43]</td>
</tr>
<tr>
<td>10% urea +1% hydrocortisone cream</td>
<td>Base cream</td>
<td>12</td>
<td>CT BL</td>
<td>QD up to 4 weeks</td>
<td>All patients treated with test agent developed softer/smooth skin</td>
<td>Burning/itching (1)</td>
<td>1968</td>
<td>[21]</td>
</tr>
</tbody>
</table>

Abbreviations: CT - controlled trial, OL - open label, CS – case series, CR – case report, BL – bilateral comparison (test versus control), QD – daily, BID – twice daily, TID – thrice daily, TEWL – transepidermal water loss

*Safety profile is only reported for test agents containing urea.

**Subjects were diagnosed with ichthyosis with a history of or present atopic dermatitis

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### Contact Dermatitis

One randomized controlled double-blinded study investigated the use of 1% hydrocortisone/10% urea/1% lactic acid (Calmuril-Hydrocortisone) cream compared to 0.05% betamethasone-17, 21-dipropionate (Diproderm) cream in 100 subjects diagnosed with contact dermatitis. Subjects were asked to rub the cream twice daily for seven days onto the affected skin; clinical assessment was performed on the first, third, and seventh days. Diproderm cream was significantly more effective than the urea-containing Calmuril-Hydrocortisone cream. Smarting was reported less frequently in patients treated with Diproderm (n=2) than Calmuril-Hydrocortisone (n=7). The authors caution to avoid long-term treatment with steroid-containing creams to minimize the risk of dermatrophia [49].

### Radiation-Induced Dermatitis

There are limited studies investigating the use of urea in the treatment of radiation-induced dermatitis. One controlled trial investigated the effects of a lotion containing 3% urea, polidocanol, and hyaluronic acid applied three times per day in 98 subjects with breast cancer to prevent acute radiation dermatitis. The control group of 174 subjects received a less intensive standard therapy. Treatment was started two to three weeks prior to radiation therapy and throughout the radiation treatment. The proportion of subjects who did not develop radiation dermatitis was significantly higher in the group that used the lotion containing urea (27.6% compared to 15.5%). The authors concluded that patients with breast cancer who received intensive use of
the lotion were half as likely to develop radiation dermatitis during radiotherapy. Only two patients reported adverse reactions during the study, one with follicular keratosis and another with an allergic reaction [50].

Psoriasis/Seborrheic Dermatitis

In psoriasis, urea improves stratum corneum hydration, water-binding capacity, and TEWL [41]. The majority of studies of urea in psoriasis were performed as part of combination therapies with dithranol. In one study, 10% urea monotherapy was found to be effective with few side effects [51]. Urea (40%) with 1% bifonazole was found to be effective in the treatment of scalp seborrheic dermatitis and scalp psoriasis [52]. Reported side effects were limited to occasional stinging and burning. An unwanted side effect that occurs when urea is combined with dithranol is the staining of the skin and clothes to a purplish brown color. The studies are outlined in Table 6 [21,41,51–62].

Table 6. Clinical studies of urea in patients with psoriasis

<table>
<thead>
<tr>
<th>Test Agent</th>
<th>Comparison Agent</th>
<th>N</th>
<th>Study design</th>
<th>Treatment Protocol</th>
<th>Results</th>
<th>Safety (N)*</th>
<th>Year</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>40% urea plus 1% bifonazole ointment</td>
<td>None</td>
<td>71</td>
<td>OL</td>
<td>Multi-month protocol</td>
<td>73.2% of patients improved after 2 weeks</td>
<td>No adverse reactions reported</td>
<td>2000</td>
<td>[54]</td>
</tr>
<tr>
<td>10% urea ointment</td>
<td>Vehicle alone or no treatment</td>
<td>10</td>
<td>CT BL</td>
<td>TID x 2 weeks</td>
<td>Urea reduced scaling, erythema and induration and increased epidermal hydration</td>
<td>No adverse reactions reported</td>
<td>1996</td>
<td>[51]</td>
</tr>
<tr>
<td>10% urea cream</td>
<td>None</td>
<td>10</td>
<td>OL</td>
<td>Observed 2h after application</td>
<td>Significant increase in water content and decrease in TEWL and hygroscopicity</td>
<td>No adverse reactions reported</td>
<td>1989</td>
<td>[41]</td>
</tr>
<tr>
<td>12% urea and 12% sodium chloride</td>
<td>Cream base</td>
<td>30</td>
<td>CT BL</td>
<td>BID x 3 weeks</td>
<td>No statistical difference between treatments</td>
<td>Burning sensation (2)</td>
<td>1985</td>
<td>[55]</td>
</tr>
<tr>
<td>12% urea and 12% sodium chloride</td>
<td>Cream base</td>
<td>40</td>
<td>CT BL</td>
<td>BID x 1 week</td>
<td>Urea cream had statistically significant improvement on scaling</td>
<td>No adverse reactions reported</td>
<td>1985</td>
<td>[56]</td>
</tr>
<tr>
<td>0.1% dithranol plus 17% urea</td>
<td>None</td>
<td>41</td>
<td>OL</td>
<td>BID x 6 weeks</td>
<td>Clinical improvement from baseline was 64% and 77% at two centers</td>
<td>Mild irritation reported; 3 patients withdrew due to dithranol-related soreness</td>
<td>1983</td>
<td>[57]</td>
</tr>
<tr>
<td>0.2% dithranol in 17% urea</td>
<td>0.1% dithranol in 17% urea</td>
<td>20</td>
<td>CT BL</td>
<td>BID x 6 weeks</td>
<td>0.2% dithranol + urea cream had improved reduction in erythema and scaling</td>
<td>2 patients withdrew due to severe irritation and burning</td>
<td>1982</td>
<td>[52]</td>
</tr>
<tr>
<td>0.1% dithranol in 17% urea cream base</td>
<td>0.1% dithranol in Lassar's paste</td>
<td>35</td>
<td>CT BL</td>
<td>QD x 4 weeks</td>
<td>No statistical difference between two treatments</td>
<td>Less inflammation, stinging, itching, discoloration with test agent at 4 weeks</td>
<td>1981</td>
<td>[58]</td>
</tr>
<tr>
<td>0.1% dithranol in 17% urea</td>
<td>Salicylic acid 2% in strong coal tar solution 10%</td>
<td>40</td>
<td>CT BL</td>
<td>BID x 6 weeks</td>
<td>No statistical difference between two treatments</td>
<td>Transient irritation and skin coloration (2)</td>
<td>1981</td>
<td>[59]</td>
</tr>
<tr>
<td>0.1% dithranol in a 17% urea base</td>
<td>None</td>
<td>20</td>
<td>OL</td>
<td>QD until clearance</td>
<td>Mean time to clearance was 8.8 days; rapid reduction in both induration and scaling within first few days of treatment</td>
<td>Staining of hair (2) and irritation in post auricular skin (3)</td>
<td>1980</td>
<td>[60]</td>
</tr>
</tbody>
</table>
0.1% dithranol plus 17% urea

17% urea base

23 CT BL BID x 6 weeks No statistical difference between two treatments Skin discoloration 1979 [53]

0.1% dithranol in a 17% urea base

8 CT BL BID x 3 weeks 54% vs. 26% clinical improvement of scaling with combination therapy vs. urea monotherapy, respectively Stinging and pain (7) and skin discoloration (1) 1978 [61]

0.1% dithranol plus 17% urea

0.05% clobetasol propionate

43 CT QD x 3 weeks Urea combination produced 80% of the clinical effect of comparison agent Stinging and skin staining 1978 [62]

10% urea cream

Urea-free base or fluocinolone acetonide ointment

5 CT BL QD x 5 days to 4 weeks Urea cream resulted in soft and pliable skin but erythema was unchanged Itching or burning (1) 1968 [21]

Abbreviations: CT - controlled trial, OL - open label, CS – case series, CR – case report, BL – bilateral comparison (test versus control), QD – daily, BID – twice daily, TID – thrice daily, TEWL – transepidermal water loss

*Safety profile is only reported for test agents containing urea.

**Onychomycosis**

Combination therapies consisting of urea with a variety of antifungal agents have been found to partially cure onychomycosis in some patients. By softening the nail bed, urea facilitates greater penetration of antifungal medications. Pretreating nails with a preparation of urea and hydrogen peroxide plus thioglycolic acid has been found to increase ungula flux of terbinafine ten fold. Moreover, this pretreatment has been found to augment the fungicidal activity of ciclopirox and amorolfine [63]. Combination therapy of urea with topical bifonazole or topical fluconazole has been shown to be clinically superior to monotherapy [64,65]. One study showed that 40% urea applied twice daily causes chemical avulsion of nails in patients with onychomycosis, facilitating the removal of fungal keratin without anesthesia or bleeding [66]. The studies are outlined in Table 7 [64–68].

**Table 7. Clinical studies of urea in patients with onychomycosis**

<table>
<thead>
<tr>
<th>Test Agent</th>
<th>Comparison Agent</th>
<th>N</th>
<th>Study design</th>
<th>Treatment Protocol</th>
<th>Results</th>
<th>Safety (N)*</th>
<th>Year</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole 1% with urea 40%</td>
<td>Fluconazole 1%</td>
<td>70</td>
<td>CT</td>
<td>QD x 6-12 months</td>
<td>Test agent produced higher rate of negative cultures and clinical improvement</td>
<td>Redness and tingling at application site (1)</td>
<td>2011</td>
<td>[65]</td>
</tr>
<tr>
<td>Solution of 1% fluconazole and 20% urea</td>
<td>None</td>
<td>13</td>
<td>OL</td>
<td>QD x 12-18 months</td>
<td>Test agent showed complete clinical cure (4) and good clinical response (8)</td>
<td>No adverse reactions reported</td>
<td>2005</td>
<td>[67]</td>
</tr>
<tr>
<td>40% Urea nail lacquer</td>
<td>None</td>
<td>10</td>
<td>OL</td>
<td>BID x 1-2 weeks</td>
<td>Test agent showed keratinolysis of nail plate, ease of affected nail removal and lack of unpleasant smell</td>
<td>No adverse reactions reported</td>
<td>2002</td>
<td>[66]</td>
</tr>
<tr>
<td>40% urea/1% bifonazole cream</td>
<td>None</td>
<td>70</td>
<td>OL</td>
<td>QD x 3 months</td>
<td>Overall 62.5% improvement rate and 50% mycological cure rate</td>
<td>Erosions (2) with one discontinuation</td>
<td>1998</td>
<td>[64]</td>
</tr>
<tr>
<td>40% urea/1% bifonazole ointment with oral griseofulvin</td>
<td>40% urea/1% bifonazole ointment or ointment alone</td>
<td>22</td>
<td>CT</td>
<td>QD x 6 months</td>
<td>Test agent produced superior response compared to either monotherapy</td>
<td>No adverse reactions reported</td>
<td>1992</td>
<td>[68]</td>
</tr>
</tbody>
</table>

Abbreviations: CT - controlled trial, OL - open label, CS – case series, CR – case report, BL – bilateral comparison (test versus control), QD – daily, BID – twice daily, TID – thrice daily

*Safety profile is only reported for test agents containing urea.

**Tinea Pedis**
Urea can decrease the fissuring and scaling associated with dermatophytoses [69]. Although urea monotherapy has been reported to have antimicrobial properties, it has also been studied in combination with antifungal creams and appears to enhance efficacy over topical antifungal monotherapy, with only rare instances of self-limited irritation. A study compared 1% lanoconazole with or without 10% urea in 43 patients with hyperkeratotic type tinea pedis. Therapy was applied daily after a bath for 12 weeks. The authors observed a 96% improvement in the combined therapy group compared to 70% improvement in the lanoconazole monotherapy group. No adverse events were reported [70]. Urea in combination with topical bifonazole[64], ciclopirox[71], or butenafine hydrochloride[72] was also found to be effective with minimal adverse effects.

## Emollient/Keratolytic

Various *in vitro* and *in vivo* studies have established the emollient and keratolytic properties of urea. Common study endpoints include reduction of TEWL, stratum corneum hydration, and clinical assessment. Urea has been shown to change certain physical properties of the skin. Early studies have shown that urea can induce conformational changes in proteins by causing unfolding, solubilization, and denaturation [73]. By possibly breaking hydrogen bonds and interfering with the quaternary structure of keratin, urea disperses and denatures keratin without disrupting the epidermal water barrier [26,74]. Several studies have also shown that urea decreases the DNA synthesis index of epidermal cells, leading to a thinning of the epidermis and reduction of basal epidermal cells. An early hypothesis was formed that pretreatment or concomitant treatment with urea can enhance efficacy of other topical therapies [75–77]. Salicylic acid is frequently combined with urea to produce a significant keratolytic effect [78]. Urea can enhance debridement in vascular and diabetic ulcers [69]. Studies investigating the emollient/keratolytic effects of urea in different skin conditions are outlined in Table 8 [14,16,33,40,41,78–85].

### Table 8. Clinical studies of the emollient/keratolytic effects of urea

<table>
<thead>
<tr>
<th>Skin Type</th>
<th>Test Agent</th>
<th>Comparison Agent</th>
<th>N</th>
<th>Study design</th>
<th>Treatment Protocol</th>
<th>Results</th>
<th>Safety (N)*</th>
<th>Year</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>40% urea in canola oil</td>
<td>Drug-free vehicle</td>
<td>78</td>
<td>CT BL</td>
<td>BID x 7 weeks</td>
<td>Test agent increased TEWL after long term exposure</td>
<td>No adverse effects noted</td>
<td>2007</td>
<td>[80]</td>
</tr>
<tr>
<td>Healthy</td>
<td>5% ammonium lactate with 3 or 5% urea</td>
<td>Drug-free vehicle</td>
<td>22</td>
<td>CT</td>
<td>BID x 7 days and then SLS irritant applied TID x 1 day</td>
<td>Test agents improved stratum corneum hydration and barrier function</td>
<td>No adverse effects reported</td>
<td>2002</td>
<td>[79]</td>
</tr>
<tr>
<td>Healthy</td>
<td>40% urea with salicylic acid</td>
<td>None</td>
<td>20</td>
<td>OL</td>
<td>Single application</td>
<td>Test agent proven keratolytic using the silver nitrate test</td>
<td>No adverse effects reported</td>
<td>2001</td>
<td>[78]</td>
</tr>
<tr>
<td>Healthy</td>
<td>10% urea + 2% salicylic acid.</td>
<td>None</td>
<td>10</td>
<td>OL</td>
<td>Single exposure followed by removal by adhesive tape</td>
<td>The degree of stratum corneum removal was not increased after 6h exposure to test agent</td>
<td>No adverse effects reported</td>
<td>1995</td>
<td>[81]</td>
</tr>
<tr>
<td>Healthy</td>
<td>Moisturizers with varying urea content</td>
<td>Urea-free vehicle</td>
<td>26</td>
<td>CT</td>
<td>Single application</td>
<td>Test agents are very potent skin humidifier and descaling agent</td>
<td>No adverse effects reported</td>
<td>1992</td>
<td>[40]</td>
</tr>
<tr>
<td>Healthy</td>
<td>10% urea/5% lactic acid/4.3% betaine (ULB); 10% urea alone</td>
<td>Base ointment</td>
<td>5</td>
<td>CT</td>
<td>QD up to 6 days</td>
<td>Only ULB cream showed penetration at days 3 and 6</td>
<td>No adverse effects noted</td>
<td>1989</td>
<td>[82]</td>
</tr>
<tr>
<td>Healthy</td>
<td>5% salicylic acid with 10% urea ointment</td>
<td>5% and 10% salicylic acid alone</td>
<td>6</td>
<td>CT</td>
<td>Single 4-hour application on back skin</td>
<td>Test agent had increased keratolysis than 5% salicylic acid</td>
<td>No adverse effects noted</td>
<td>1987</td>
<td>[83]</td>
</tr>
<tr>
<td>Hyperkeratotic</td>
<td>30% urea emollient foam</td>
<td>None</td>
<td>10</td>
<td>CS</td>
<td>BID x 4 weeks</td>
<td>Significant improvements in skin condition and patients' ratings of quality of life</td>
<td>No adverse effects noted</td>
<td>2008</td>
<td>[84]</td>
</tr>
<tr>
<td>Psoriatic</td>
<td>10% urea cream</td>
<td>None</td>
<td>20</td>
<td>OL</td>
<td>Observed 2h after application</td>
<td>Test agent improved stratum corneum hydration, water-binding capacity, and TEWL</td>
<td>No adverse effects reported</td>
<td>1989</td>
<td>[41]</td>
</tr>
</tbody>
</table>
### Pruritus

There is limited evidence that topical urea application can improve symptoms of pruritus. An early study investigated the antipruritic effects of two urea solutions and their urea-free placebos. Patients with pruritic dermatoses received intradermal injections of trypsin as an irritant followed by a measurement of the duration of itch sensation. Thereafter, test or placebo solution was applied followed by a second round of trypsin injections and measurement of itch duration. The urea solutions provided a significant prophylactic antipruritic effect when compared to placebo in every case [86].

In a separate clinical study, 15 patients with pruritic dermatoses were asked to apply a urea solution to pruritic skin and instructed not to reuse the solution until itching returned. Pruritus resolved within minutes for the majority of patients and most patients expressed satisfaction with the antipruritic effect [86].

### Chemical Nail Avulsion / Dystrophic Nails

Urea 40% has been used successfully under occlusion to achieve chemical avulsion of the nail in a number of studies. An early study with 35 patients showed that both 22% and 40% urea applied under occlusion could avulse nails in less than 10 days [87]. Non-dystrophic nails were not affected. Infrequent and transient side effects of maceration and irritation were reported. In onychomycosis, once the dystrophic nail is removed, subsequent treatment with topical antifungal drugs is facilitated. The failure to achieve avulsion is usually owing to lack of gross nail dystrophy, inadequate occlusion of the dressing, water immersion by the patient, and/or the use of an outdated urea preparation. Benefits of chemical over surgical avulsion include decreased risk of bleeding and infection as well as enhanced function [88].

### Penetration Enhancement

A number of studies support the capacity of urea to enhance penetration of drug substances into the skin. A variety of substances have been studied, including topical steroids and topical antifungal drugs. Urea is thought to alter the physical and chemical properties of keratin, enhancing permeation of mono-substances. Urea can also alter the permeation kinetics of the horny layer of the skin by changing the binding capacity, leading to decreased penetration and increased retention time [89].

Many studies have looked at the concomitant use of urea in topical steroid application. An early study assessed the penetration of topical cortisol in four different vehicles: 10% urea in a cream base, 10% urea in a stabilizing emulsified base, and two control creams. The skin of a pig was used. The urea-cream base penetrated the skin with a 30-fold increase in efficacy compared to the emulsified base [90]. A second study found that 10% urea increases the penetration of hydrocortisone and triamcinolone acetonide by 50%, increasing the therapeutic effect of the drugs [91]. A third study used a powder-cream base containing a hyperosmolar urea solution absorbed in starch granules, suspended within a continuous lipid phase of an aqueous-lipid emulsion incorporating 1% hydrocortisone. When tested in adults, the vehicle increased efficacy and increased penetration of hydrocortisone, producing an effectiveness comparable to that of 0.1% betamethasone-17-valerate [44]. An in vitro study using guinea pig skin, however, showed that 10% urea decreased the percutaneous absorption of hydrocortisone [92].
Conclusion

Urea has been used safely and effectively in large populations of patients across a wide variety of disease settings. Urea is moisturizing and keratolytic, making it useful in diseases of dry and scaly skin such as ichthyosis, xerosis, and psoriasis. Urea enhances skin penetration and overall clinical benefit of other drugs such as corticosteroids and antifungals when used concomitantly. Urea therapy has been associated with few adverse effects and is generally well tolerated. Both the safety and efficacy of urea have been largely established over the past hundred years and urea should continue to be considered by clinicians as a viable treatment option for patients.

References


0.1% dithranol and 17% urea in a cream base and 0.1% dithranol in Lassar’s past B.P.C. Acta Derm. Venereol.
60. Hindson TC. Treatment of psoriasis of the scalp: an open assessment of 0.1% dithranol in a 17% urea cream base
61. Buckley DB. A double-blind comparison of 0.1% dithranol in a 17% urea base (“Psoradrate”) and base alone in the
0.1% dithranol plus 17% Urea (Psoradrate) and 0.05% Clobetasol Propionate (Dermovate). Clinical Trials Journal.
63. Baran R, Coquard F. Combination of fluniconazole and urea in a nail lacquer for treating onychomycosis. Journal of
64. Shemer A, Bergman R, Cohen A, Friedman-Birnbaum R. [Treatment of onychomycosis using 40% urea with 1% bifonazole].
Harefuah. 1992 Feb 2;122(3):159–160. [PMID: 1532948]
66. Tanuma H, Tanuma M, Abe M, Kume H. Usefulness of lanoconazole (Astat) cream in the treatment of hyperkeratotic type
tinea pedis. Comparative study of monotherapy and combination therapy with 10% urea ointment (Pastaron). Mycoses.
May;73(5):355–357. [PMID: 15186053]
hyperkeratotic type tinea pedis and its transfer into the horny layer, with or without concomitant application of 20% urea
[PMID: 5548481]
71. Woehr W, Wohlrab W, Scharnemann S. [Investigations on the mechanism of the activity of urea upon the epidermis (author’s transl)]. Arch
74. Gloor M, Fluhr J, Wasik B, Gehring W. [Clinical effect of salicylic acid and high dose urea cream applied according to the
75. Gloor M, Fluhr J, Lehmann L, Gehring W, Thieroff-Ekerdt R. Do urea/ammonium lactate combinations achieve better skin
11803256]
76. Buraczewska I, Berne B, Lindberg M, Törmä H, Loden M. Changes in skin barrier function following long-term treatment
77. Lodén M, Boström P, Knezeck M. Distribution and keratolytic effect of salicylic acid and urea in human skin. Skin
9:63–66. [PMID: 2807926]
80. Goldstein JA, Gurge RM. Treatment of hyperkeratosis with Kerafoam emollient foam (30% urea) to assess efectiveness and
2245997]


