What evidence is there for moisturisers?

A review of the available evidence for various ingredients in products recommended as moisturisers in dry skin conditions. This article is intended to accompany a CPD article on the mechanisms involved in dry skin conditions published on 2 April 2011

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Given the widespread use of moisturisers there are surprisingly few good quality studies of efficacy in patients. Some studies show that some of the more common ingredients used do increase skin hydration or improve the barrier function of the skin (ie, reduce transepidermal water loss; TEWL). However, even where studies exist, one of the problems for investigators is the lack of a standardised definition of dry skin that can be measured objectively. In addition, studies tend to be small — often with around 30 subjects.

Many studies use changes or differences in TEWL or capacitance as measures of effectiveness, but changes in symptom scores are often a better indicator. TEWL is not a sensitive measure and has been shown to either increase or decrease after the application of various moisturisers. Indeed, improvement in symptoms does not always correlate with a reduction in TEWL. Some studies in people with xerotic skin have included visual analogue scales and expert assessment in addition to the biometric methods as part of the evaluation process.

Glycerol

Glycerol (glycerin) is an old-fashioned humectant widely used in cosmetic preparations. It also occurs naturally in skin and is transported to the stratum corneum via aquaporin 3 (AQP3) channels, which are membrane based transporter molecules in the basal keratinocyte layer.

KEY POINTS

- There is a lack of good quality clinical trials on moisturising products but there is evidence of benefit from using moisturisers in eczema and psoriasis.
- Alpha hydroxy acids (eg, lactic acid) appear to have an effect on desquamation, making them helpful in scaling conditions.
- Some evidence suggests that long-term use of moisturisers on normal skin may have adverse effects, such as increased sensitivity to irritants.
- Aqueous cream should not be considered as a first-line, leave-on emollient.
- Newer moisturisers are beginning to include barrier repair lipids (eg, ceramides).
- Patients with dry skin conditions should be given a wide choice of products to encourage frequent use.

The importance of glycerol in skin hydration has been clearly demonstrated in rodent studies in which animals lacking the AQP3 channels have dry skin. Topical and oral administration of glycerol improved dry skin and a similar effect has been suggested in humans. The hydrating effect of topical glycerol has been shown to be maintained over six weeks compared with placebo.

Another role of glycerol is that it aids desquamation and one study, although *in vitro*, showed that it increased the rate of corneocyte loss by facilitating corneodesmosome breakdown.

However, there are few good quality clinical trials of glycerol in patients with dry skin conditions. In 2008, a randomised, double-blind prospective study in patients with mild-to-moderate atopic eczema found that application of a 20 per cent glycerol cream improved skin hydration compared with placebo but there was no significant difference in erythema and SCORAD (an eczema severity score) values between the glycerol group and the control group.[1]

An earlier double-blind trial in 197 patients with atopic eczema found a 20 per cent glycerol cream to be equivalent to a cream containing both urea (4 per cent) and sodium chloride (4 per cent) but that the glycerol cream produced less smarting.[2] Findings were based on patient self-reporting and independent evaluation by a dermatologist. Although there were no significant differences in dryness scores between the two groups, 11 per cent of patients in the urea group reported drier skin after using the urea. In another clinical study in atopic patients by the same researchers, it was found that the same urea cream (rather than the glycerol) provided greater reduction in TEWL and lower aggregated dryness scores.[3] The authors noted that the changes in skin capacitance were not different for the two test creams and results with the glycerin cream were not significantly different to placebo.

A recent study found glycerol to be beneficial in reducing the irritation from surfactant induced contact dermatitis.[4]

Urea

Urea is an ingredient seen in many moisturisers, including Balneum and E45 Itch Relief (5 per cent), Aquadrate, Calmurid, Eucerin Intensive and Hydromol Intensive (10 per cent) and Dermatonics Heel Balm (25 per cent). A double-blind comparison of two creams containing 3 or 10 per cent urea found both equally effective at increasing hydration and reducing scaling associated with dry skin.[5]

In a study of patients with atopic eczema, it was found that twice daily application of 5 per cent urea for 20 days reduced TEWL and the susceptibility of the skin to sodium lauryl sulphate (ie, barrier function was improved).[6] In another study a 10 per cent cream reduced TEWL and improved the itching and dryness associated with atopic eczema.[7] →

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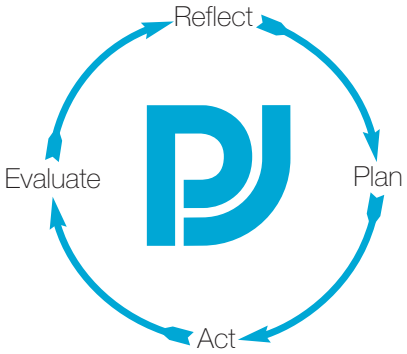

REFLECT

1 Which ingredients in moisturiser products have evidence of efficacy?
2 What is the rationale for using oatmeal extracts for dry skin conditions?
3 Are you confident of the advice you give to people with dry skin?

Before reading on, think about how this article may help you to do your job better.

A randomised, double-blind trial in children with ichthyosis found that a 10 per cent lotion improved the clinical signs of the condition based on a visual analogue scale, but the differences were small[8] (78 per cent response rate vs 72 per cent in the placebo) and the results of the capacitance measurements were similar.

A urea based lotion was also found to reduce the symptoms of dry skin and itching in a randomised, double-blind study compared with the vehicle base in aged skin.[9]

Oatmeal extracts

Some evidence exists to show that colloidal oatmeal is effective in the management of dry skin. Colloidal oatmeal contains lipids, proteins and polysaccharides and when dispersed in water, it forms a viscous occlusive barrier and the hydrophilic polysaccharides absorb water, creating a humectant effect. The proteins present also provide a buffering action, which helps to lower skin pH in pruritic conditions. One study using an oatmeal lotion (Aveeno) in patients with itching due to skin lesions and dryness found that the lotion provided relief of symptomatic itch in over 80 per cent of patients.[10]

There is some evidence that oatmeal extract reduces release of arachidonic acid from phospholipids, suggesting an anti-inflammatory effect. In particular, in 2005, a study using avenanthramides (phytochemicals found in oatmeal) showed that when used topically, these agents have a potent anti-inflammatory effect.[11]

One study with oatmeal extracts has shown a significant reduction in irritation from application of sodium lauryl sulphate, which suggests a potential role for oatmeal products in contact dermatitis.[12]

B vitamins

Pantothenic acid (vitamin B5) is a component of co-enzyme A that is essential to the normal functioning of keratinocytes. There has been interest in nicotinamide, a vitamin B analogue, because it has been shown to increase ceramide synthesis and reduce TEWL in dry skin. It has also been shown that application significantly reduced TEWL compared with petroleum jelly in atopic eczema.[13]

Dexpanthenol (the active ingredient in Bepanthen) is an alcoholic derivative of pantothenic acid and is often used as a humectant. Used topically for seven days in a randomised, double-blind placebo controlled study, dexpanthenol improved stratum corneum hydration and reduced TEWL.[14] In a second randomised, double-blind study with patients who had atopic eczema, ichthyosis, psoriasis or contact dermatitis, dexpanthanol (3 per cent) treatment for four weeks led to a greater than 80 per cent improvement in symptom scores.[15]

Alpha hydroxy acids

Alpha hydroxy acids are included in moisturisers because they are thought to facilitate desquamation, making them particularly valuable in hyperkeratotic disorders. The alpha hydroxy acids typically used include lactic acid (a component of natural moisturising factor) and glycolic acid. One recent study in hairless mice showed that repeated application of lactic acid 5 per cent or glycolic acid 5 per cent over 14 days did not change TEWL or capacitance but produced an increase in secretion of lamella bodies and a decrease in the number of stratum corneum layers, (ie, enhanced desquamation) compared with the untreated group. Other studies have suggested that as well as enhancing desquamation, the acids are also incorporated into the lamella bodies and this leads to an increased ceramide synthesis and a stronger barrier.

There are several studies, some that are randomised and double blind, using the alpha hydroxy acids in dry skin. In many studies, lactic acid is formulated as the sodium or ammonium salt. In short, most suggest that lactic acid is an effective moisturising agent, leading to improvements in skin hydration although some also suggest that lactic acid based moisturisers are no more effective than simple occlusive agents such as lanolin.

Sodium pyrrolidone carboxylic acid

Sodium pyrrolidone carboxylic acid (PCA) is a component of natural moisturising factor. It is formed from filaggrin-derived free amino acids. In the skin it is more likely to exist as the ammonium salt. PCA is dramatically depleted in conditions such as psoriasis.

Although there are few clinical studies demonstrating this agent improves xerotic skin, one study has shown that a 5 per cent sodium PCA cream improved hand dryness in women when used for up to six weeks. However, the cream was not superior to an alternative containing urea. No other details of the cream were provided.[16]

Hyaluronic acid

Hyaluronic acid is a glucosaminoglycan (carbohydrate polymer) which is present in several tissues in the body and is a well known component of cartilage. This compound is often found in anti-ageing creams and some commercial moisturisers. There do not appear to be any studies of hyaluronic acid as a moisturiser but there is some evidence of a role in epidermal hyperplasia, which occurs after damage to the barrier with acetone.[17]

More recent products

Studies on skin barrier recovery after treatment with acetone have shown that after application of a mixture of physiological lipids, those lipids were incorporated into epidermal cells and processed for secretion in the barrier repair process. It has been suggested that the replacement of physiological lipids via moisturisers, might improve atopic eczema.

In a recent study in mice models of inflammation and atopic dermatitis, topical

PANEL 1: RECENT FDA APPROVED MOISTURISERS

EpiCeram EpiCeram Skin Barrier Emulsion is a mixture of ceramides, cholesterol and fatty acids, mimicking those in the skin. Two studies have reported on its effects. One was published as a full paper but the second is available only as an abstract. The first compared EpiCeram against fluticasone proprionate in children with moderate-to-severe atopic eczema. The results showed that, although fluticasone produced a faster response, the difference was not significant after 28 days of therapy.[20] The second study was prospective, randomised and investigator blinded. It compared EpiCeram with pimecrolimus in 38 children with mild-to-moderate eczema. The primary outcome measure was the change in EASI scores (an eczema severity scale). After four weeks, the pimecrolimus group achieved a median reduction in EASI score of 2.0 compared with 1.2 for pimecrolimus but this difference was reported as not significant.[21]

EpiCeram is not currently available in the UK.

Atopiclair The ingredients of Atopiclair are botanical and include glycyrrhetinic acid (from liquorice), grape seed oil and shea butter. The product was approved for atopic dermatitis, contact dermatitis and dry skin. There are three published randomised, double-blind vehicle-controlled trials in patients with atopic eczema, all of which show superiority of Atopiclair.[22–24] Presumably the efficacy is based on a combined effect of the components so the use of a valid vehicle control in trails is difficult. This product, which also contains hyaluronic acid, is available in the UK.

MimyX MimyX contains the fatty acid N-palmitoyl ethanolamine, a potent agonist of cannabinoid receptors on mast cells. Cannabinoid receptors are also present on keratinocytes. N-palmitoyl ethanolamine exhibits strong anti-inflammatory effects in animal models. It was approved for the management of atopic dermatitis, allergic contact dermatitis and radiation dermatitis. Although there are no published clinical studies available on the product itself, one study of N-palmitamoyl ethanolamine in mild-to-moderate atopic eczema found patients reported a reduction in pruritus and skin dryness, and that scaling was reduced.[25] MimyX is not currently available in the UK.

The author will be available to answer questions on this topic until 2 May 2011

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PANEL 2: EVIDENCE FOR MOISTURISERS IN ECZEMA

Studies with moisturisers have shown that it is possible to reduce the time to relapse in atopic eczema once the condition has been brought under control with the use of a topical corticosteroid. Grimalt *et al* showed, in a randomised trial with 173 children, that use of an emollient in moderate to severe atopic eczema for six weeks led to a significant improvement in SCORAD score and a reduction in topical steroid use.[33] In addition, Berth-Jones *et al* found that emollient use reduced the time to relapse requiring corticosteroid use to six weeks.[34]

In a study using methylprednisolone aceponate cream in patients with atopic eczema, Peserico *et al* found that the probability of not experiencing a relapse when using only an emollient was 65.8 per cent after 16 weeks.[35] Another study, of atopic eczema in children, found that using the vehicle of tacrolimus (ie, an emollient) alone, the time to relapse was 38 days (compared with 173 days with tacrolimus) and there were no differences in quality of life scores between vehicle and active treatments.[36]

Finally, Cork *et al* found that increased patient education regarding the appropriate use of moisturisers led to an 800 per cent increase in moisturiser use and a corresponding 89 per cent reduction in the severity of the eczema.[37] It is clear, therefore, that moisturisers have a potentially valuable role to play in the management of atopic eczema.

application of a ceramide-containing mixture suppressed inflammation. However, there is only one published study on the use of topical ceramide mixtures in atopic eczema patients: Chamlin *et al* found that when children substituted their usual moisturiser with a physiological ceramide mixture (other therapies were continued), severity scores for eczema improved significantly.[18] However, although potentially effective in atopic eczema, a study using skin identical lipids compared with petroleum jelly in tape and detergent stripped skin, found no difference between either preparation.[19]

The US Food and Drug Administration recently approved the products in Panel 1.

Selecting a moisturiser

It has been estimated that the adherence rate with topical treatment is between 55 and 66 per cent.[26] In eczema, moisturisers should be applied as often as needed — this could be six or seven times a day. It is important, therefore, that patients are given adequate choice over preparations because unacceptable products are unlikely to be used.

Patient factors that influence choice are independent of clinical efficacy and include how the product feels on the skin, whether or not it is easily absorbed through the skin, and how it smells. Ideally, a moisturiser should also be hypoallergenic and non-comedogenic.

The market is split into products for facial hand, foot or body use. The heaviness or thickness of a formulation relates to the amount of occlusive agents present and this can dictate how the product will be used. For instance, night-time creams are often heavier. A facial cream will typically consist of as much as 80 per cent water, 5 per cent humectant (usually glycerin) and 4 per cent occlusives or emollients. Moisturisers for body and hand use will typically contain slightly more water (85 per cent) and slightly less occlusives and emollients, although content can be as high as 44 per cent.

The skin on the face receives the most exposure to the environment. It has a thinner stratum corneum and poorer barrier function than other parts of the body as noted by higher TEWL. In addition, facial skin contains a higher proportion of lipids, which are easily removed by washing with soap. The evidence for efficacy for facial moisturisers is almost non-existent except for one study, which showed that daily application of a moisturiser to the face in winter improved hydration and reduced TEWL.[27] Any moisturiser designed for use on the face is normally a cream or lotion and will tend to be non-greasy and non-comedogenic. The "shine" observed with greasy skin can be alleviated by the use of products containing agents, such as kaolin or talc, which absorb excess sebum.

Benefits and adverse effects

With such scarce good quality evidence, readers may wonder if moisturisers are a waste of time. Moreover, adverse effects (in addition to allergies) have been reported and some creams may worsen symptoms. Last year, it was found that aqueous cream containing around 1 per cent sodium lauryl sulphate reduced the thickness of healthy skin and increased its permeability to water loss over four weeks.[28] Sodium lauryl sulphate is able to reduce the stratum corneum thickness of normal skin significantly following repeated yet brief application. Although aqueous cream was originally designed to be used as a wash product (hence with a short contact time), the cream is used by many patients as a cheap leave-on emollient. A blanket restriction on creams containing sodium lauryl sulphate is unwise but aqueous cream should not be considered as a first-line leave-on emollient. When used as a wash, it causes few problems.

The impact of long-term use of moisturisers on normal skin has recently been studied and has shown some alarming adverse effects such as an increase in TEWL, reduced capacitance (ie, greater dryness) as well as increased sensitivity to irritants.[29] These observations concur with some earlier work demonstrating that application of a moisturiser with a high lipid content (70 per cent) for 30 days to normal increased the susceptibility to sodium lauryl sulphate[30] and nickel sulphate.[31] These studies suggest that differences in moisturiser composition can potentially alter skin barrier function rendering the skin more sensitive to external irritants. Whether or not such effects would occur in xerotic or diseased skin is unclear. However, a recent review has suggested that moisturisers have an important role in the management of psoriasis[32] and the National Institute for Health and Clinical Excellence has recommended that moisturisers should be used daily in children with atopic eczema. This conclusion seems to be based on a consensus of clinical experience rather than direct clinical evidence (see Panel 2).

Summary

There is evidence that moisturisers can relieve dryness induced by changes in temperature and relative humidity or associated with conditions such as eczema and ichthyosis. It seems likely that glycerol and urea are probably effective hydrating agents although the data from clinical studies are ambiguous. Alpha hydroxy acids appear to have a noticeable effect on desquamation and this is likely to be due to facilitation of corneodesmolysis. There is little evidence to show superiority for any specific agent but such agents are likely to be of value in hyperkeratotic skin conditions (eg, psoriasis).

There is a lack of suitable clinical studies to draw any firm conclusions regarding the wide range of other chemical entities included in moisturisers but the evidence that is available, appears to suggest that increased hydration occurs when these agents are used.

There is no evidence from the literature to recommend any particular preparation. It is up to the pharmaceutical and cosmetic industry to provide more clinical information based on patient studies if healthcare professionals are to be convinced that a specific formulation is superior to its competitors.

PRACTICE POINTS

Reading is only one way to undertake CPD and the regulator will expect to see various approaches in a pharmacist's CPD portfolio.

1 Target medicines use reviews at patients with eczema or psoriasis this week.
2 With a colleague choose your top three moisturisers, listing advantages and disadvantages.
3 Take time to ask patients for feedback on products and use this to inform your recommendations.

Consider making this activity one of your nine CPD entries this year.

Learning & development

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