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Abstract

Atopic eczema (AE) is one of the most common dermatological diseases, with the number of cases in the UK rising. The use of emollients to maintain skin hydration and restore barrier function remains the principal treatment, in conjunction with topical corticosteroids (TCS) to reduce inflammation. Unfortunately, many health professionals, and patients themselves, fail to consider emollients an active treatment and may overlook the vital role they play in the maintenance of intact, healthy skin. Despite the overwhelming acceptance of the importance of emollient therapy, there remains a lack of good quality evidence on their effectiveness or whether one is better than another. Patients often receive conflicting or limited advice from health professionals as to how to use them, and if using TCS as well, which to apply first. This may result in incorrect use, reduced therapeutic effect and poor concordance. This article aims to explore normal skin barrier function, the disruption caused by AE, and some of the contemporary issues surrounding emollient therapy and topical corticosteroids.

Key Words: Atopic eczema, Atopic dermatitis, Eczema, Skin barrier, Emollients, Topical corticosteroids.

Introduction

It is suggested that just over half the UK population will experience a skin disorder in a given 12-month period (Schofield *et al* 2009). Whilst most of these individuals will initially self-care, buying treatments over the counter (OTC), a significant number will seek medical advice, with skin complaints accounting for approximately 15% of GP consultations (APPGS 2013). The commonest complaint seen is atopic eczema (AE), also known as atopic dermatitis, affecting up to 20% of children and 3% of adults (Nutten 2015). Atopic eczema is a chronic inflammatory disease that disrupts the skin barrier, causing the skin to become inflamed, itchy, dry and cracked. The advances made in our understanding of the immunological mechanisms involved in AE has led to an increase in topical treatments available, ranging from more sophisticated emollients through to novel immunomodulators. However, the use of emollients to maintain skin hydration and topical corticosteroids to reduce the inflammation, remains the first-line in treatment. The management of AE requires the regular application of topical treatments, which are time-consuming and onerous for patients, families and carers. These are often accompanied by poor or vague instructions from the prescriber, particularly with respect to the timing and order of product application. Not surprisingly, the combination of complex regimens and inconsistent advice can lead to poor concordance, resulting in suboptimal management and wasted prescription items.

Normal Skin Barrier Function

One of the major functions of healthy skin is the maintenance of a physical barrier against the external environment. This prevents the entry of harmful substances and pathogens, as well as preventing excessive fluid loss from the body. This is achieved by the uppermost layer of the skin, the epidermis and in particular the outermost part of the epidermis, the stratum corneum (Figure 1). The stratum corneum is

composed of several layers of flattened, dead cells called corneocytes. These cells are held together by a mixture of lipids in a 'bricks and mortar' arrangement to form an effective barrier (Rawlings 2010). There is a constant supply of new corneocytes from the lower epidermal layers with cells taking approximately 14 days to migrate from the lowest layer of the epidermis and a further 14 days before they are shed from the skin surface in a process known as desquamation (Clark 2004). Normally, corneocyte desquamation is in balance with the replacement of new corneocytes, so that it is not noticeable. In normal health, the structure and barrier function of the stratum corneum is maintained and regulated by a complex system of proteins and other substances. The protein filaggrin binds to keratin, enabling the formation of the densely packed lipid-protein matrix that provides the scaffold that holds the corneocytes together to give the stratum corneum its structure (Sandilands et al, 2009). Barrier function is also promoted by substances in the corneocytes known as natural moisturizing factor (NMF), which is also influenced by filaggrin. NMF is a complex mixture of free amino acids, amino acid derivatives and salts, which attract and hold water within the corneocytes. This increase in intracellular water helps the corneocytes to retain their turgidity and shape, thus maintaining a coherent barrier. This also helps to maintain skin flexibility and elasticity by absorbing water from the atmosphere, which enables the outermost layers of the skin to remain hydrated, despite the drying action of the environment (Rawlings and Harding, 2004). Further studies have highlighted the importance of another group of proteins, collectively known as aquaporins, in the regulation and maintenance of skin hydration. These form channels which help regulate the flow of water within cells and are found throughout various tissues in the body (Day et al, 2014). In the epidermis aquaporin 3 and 10 play an important role in water balance, and are also involved in the movement of glycerol and urea, both

important substances in helping the skin retain moisture (Soler et al, 2015). The early work by Olsson et al (2006) demonstrated altered aquaporin levels in the skin of patients with atopic eczema, particularly of aquaporin 3, and this imbalance is thought to contribute to the rapid and severe formation of dry skin seen in this condition.

Atopic eczema and skin barrier function.

Like other western countries, the UK has seen an increase in the incidence of AE making it one of the most common dermatological disorders. The majority of individuals (70-80%) will suffer from true AE, mediated by immunoglobulin E (IgE) and linked to other allergic responses, whilst the remainder (20-30%) have a non-atopic variant, not linked to allergic mechanisms (Leung et al 2004). However in both atopic and non-atopic eczema the familiar mixture of genetic and environmental factors working together, as seen in other conditions, appears to be important in disease development. AE commonly affects the face, elbows, backs of the knees and the neck. Visually the affected skin appears dry, inflamed, cracked and thickened. If severely dry, cracks and fissures may be visible, and the surrounding skin may also appear red indicating the presence of inflammation and possible secondary infection. The skin feels rough and uneven to touch, and the patient may complain of a feeling of tightness. This may be accompanied by sensory changes such as tingling, itching or even stinging and pain. Physiological changes are also observed, with the stratum corneum of dry skin containing less water and natural moisturising factor (NMF) than that of healthy skin. The healthy stratum corneum has a relatively high water content of 15-20% and if this falls to less than 10% the skin surface shows fine scaling and feels rough (Clark, 2004). Low intercellular lipid levels in the stratum corneum,

particularly ceramides, have been found in patients with AE (Di Nardo et al, 1998; Imokawa and Ishida, 2014).

In normal skin NMF is found in abundance in the corneocytes, and accounts for up to 20% of the weight of the stratum corneum. Low levels of NMF are associated with severe cases of xerosis, and filaggrin levels have also been shown to fall with increasing age leading to a reduction in NMF production (Takahashi and Tezuka, 2004). It has also been demonstrated that mutations in the gene responsible for the production of filaggrin are present in individuals with the common dry skin condition of ichthyosis vulgaris, and are also implicated in the development of AE. The mutations lead to a reduction in filaggrin content in the stratum corneum, disrupting the normal homeostatic mechanisms that maintain stratum corneum structure and skin hydration, consequently severe drying and flaking of the skin occurs (Nomura, 2007). More recently, cohort studies investigating mutations of the filaggrin gene in adults and children, have demonstrated differences between ethnic groups and in responsiveness to treatment (Margolis et al, 2012). Whilst further gene polymorphisms have been linked to abnormal immune responses in AE (Saunders et al, 2013). Ultimately eczematous skin is unable to provide the protective barrier function essential for health. It is more permeable, leading to high levels of transepidermal water loss (TEWL) and has a reduced ability to resist the absorption of substances that may come into contact with the skin surface, or the entry of microbes (Proksch et al, 2008).

Dermal absorption of topical preparations.

Healthy, intact skin provides an effective barrier to the absorption of many chemicals, including drugs. However, to achieve their effect, topically applied products must

pass across the skin barrier and distribute throughout the skin layers. Some drugs are more capable of doing this than others. Typically, small molecules that are primarily lipophilic, but which also have some hydrophilic properties, are able to penetrate the skin best, passing into the stratum corneum by simple diffusion (McAuley and Kravitz, 2012). The permeability of the skin to topically applied drugs varies between anatomical location, with the skin of the genitals and face being more permeable to drug absorption than the limbs or abdomen (Wester and Maibach 2005). The number of hair follicles in the skin also plays a part, with hydrophilic drugs being able to pass down the hair follicle and diffuse through into the skin (Ogiso et al, 2002). In most cases, the physiochemical properties of the drug (e.g. molecule size, solubility) prevent it from diffusing across the skin barrier without some help. This can be achieved by changing the drug's chemical properties (and hence solubility) or adding penetration enhancers to the formulation (e.g. propylene glycol, ethanol, isopropyl myristate) which help 'carry' the drug across the skin barrier (McAuley and Kravitz, 2012). Another way to increase drug absorption into the skin is the use of occlusion. If the skin surface is occluded (e.g. by a film dressing or ointment) transepidermal water loss is restricted, leading to increased hydration of the stratum corneum, and increased permeability (Zhai and Maibach, 2001). Obviously if the skin is inflamed, as in AE, then the effectiveness of the normal barrier will be reduced. Thus, topical drug absorption will be different in areas affected by skin disease, and in most cases will be significantly higher.

Composition of Emollients, TCS and Actions.

The term emollient is derived from the Latin meaning to soften, and implies a substance that acts to smooth and hydrate the skin. Current emollients are available in

the form of sprays, lotions, creams and ointments. Whatever form they take, the basic principle remains the same, namely they are all variations of an oil (lipid) and water emulsion. The immediate effect of an emollient is to add an occlusive lipid layer to the skin surface, the intermediate effect is the addition of lipid to the intercellular spaces and a delayed effect is the provision of lipids to the epidermal cells themselves (Teichmann et al., 2006). Emulsifying agents and surfactants (e.g. cetostearyl alcohol, isopropyl myristate) are commonly added to increase product stability and enabling the use of less oil, therefore reducing the overall greasiness of the emollient, making it more acceptable to the patient. In simple terms as an emollient moves from being a lotion to a cream, to an ointment, so the oil content increases. Care must be taken with paraffin-based ointments due to the increased fire risk. This risk has been highlighted in safety alerts issued by the MHRA (2016) in patients being treated with paraffin-based emollient products that are covered by a dressing or clothing. There is a danger that smoking or using a naked flame could cause the dressing or clothing to catch fire. Patients should also be advised to change their clothing and bedding regularly as the paraffin can soak into fabrics, again becoming a fire hazard. In order to increase the moisturising effects of emollients additional agents, known as humectants, may be added, (e.g. propylene glycol, urea, and glycerol). These tend to be hygroscopic chemicals, which attract and absorb water from their surroundings, thus helping to attract water into the stratum corneum when applied topically (Voegeli 2011). The rich mixture of lipid and water makes an ideal breeding ground for bacteria, so in many cases agents to inhibit bacterial growth are needed (e.g. Benzalkonium chloride, hydroxybenzoates). Sensitivity to these additives may occur exacerbating the original problem (Table 1), and should be considered should the skin condition worsen even

with a seemingly simple preparation, as illustrated by the MHRA (2013) alert concerning aqueous cream.

Although emollients have always been the cornerstone of dermatological treatment, there is little high quality evidence to demonstrate the beneficial effects of emollient therapy in the management of AE and little to guide the choice of emollient. In most cases the decision of which one to use is largely influenced by local formulary and cost, or patient preference. It has been stated that the most effective emollient is the one that the patient likes and therefore will actually use (Burr 1999).

In contrast, the evidence supporting the use of TCS in AE is of better quality, with a recent systematic review concluding that once daily application of TCS provided reasonable benefit in disease management (Nankervis et al, 2016). There is some acknowledgement that the base of the TCS (cream or ointment) may influence efficacy, but little evidence about the actual effect of an emollient on TCS absorption and steroid concentration levels in the skin (Smoker and Voegeli, 2014). The synergistic relationship between TCS and emollients is well known, with effective emollient therapy having consistently been shown to have a 'steroid sparing' effect (Harcharik and Emer, 2014).

Patient Education.

Despite the acknowledgement of the widespread benefits of emollients and TCS in the management of AE, there is no firm evidence base regarding the sequence of applying emollients and topical steroids. This often leads to confusion amongst healthcare professionals, with patients receiving conflicting advice on how to apply their products. Two main arguments exist, the first argues that the emollient should be applied before the steroid, and the second suggests that the steroid should be applied

before the emollient. Unfortunately the answer is not clear cut, as evidence exists in support of both arguments. Flohr and Williams (2004) in a review of the management of atopic eczema found evidence for applying emollients before the topical steroid (to ensure that the stratum corneum is well hydrated and therefore make it easier for the steroid to enter the skin), and for applying topical steroids prior to emollients to reduce the risk of diluting the topical steroid. In both situations it is suggested that a variable period of time is allowed between each application, and again the advice offered varies and has been debated for the last 15 years, as summarised in table 2 (Smoker and Voegeli, 2014). Flohr and Williams (2004) recommended leaving a gap of one hour between applying the steroid first, and then the emollient. Whilst Gradwell and McGarvey (2006) suggested steroids should be applied at least 30 minutes after emollients. The debate on which product to apply first when using TCS and emollients together continues, and the effect of this on professional practice was nicely highlighted in a survey of whether dermatology nurses applied emollients before or after other topical applications; 48% replied before, 30% after and 22% at the same time (Penzer, 2005). Since 2010 prescribing and professional advice (PCDS 2016) has moved towards advising applying an emollient first and then the steroid after a 15 – 30 minute gap, although Moncrieff et al (2013) suggests that the order of application makes no difference. However, the fact that this guidance is based on low quality evidence, and that there have been no robust studies in this area is often forgotten. This gap in our knowledge has been acknowledged by NICE (2007), who state that the order of application is not known, and more recently this topic has been identified as a priority area for research by both patients and professionals (UKDCTN, 2012). With these debates continuing, it is not surprising that patients receive inconsistent advice, which may affect concordance with treatment plans.

Conclusion.

Both TCS and emollients have important and well-established roles in the management of atopic eczema. Despite this, gaps continue to exist in the evidence base for both, and in particular with how both should be used together. Expert consensus has shifted towards recommending emollients are applied before TCS, or ignoring the question altogether and taking a pragmatic view, in that the order is irrelevant and getting the patient to use the products being more important. Unfortunately the guidance on how long to wait between products is less clear, with the 15 - 30 minute gap appearing to be more 'tradition' rather than based on any firm evidence. Ultimately, in order to achieve maximum concordance any treatment plan must be both acceptable to the patient and manageable within the context of their daily life, therefore a pragmatic approach is often required. By understanding some of these issues nurses can be in a better position when advising patients, so promoting effective use and concordance with treatments. There is clearly a case for challenging existing ritual and dogma because of the inconsistency and confusion surrounding current practices, whilst at the same time acknowledging the potential for greater simplicity in skin care regimes. This requires well-designed research, which addresses and answers questions of relevance to both patients and professionals.

Key Points

- Atopic eczema is one of the most common dermatological diseases, with the number of cases in the UK rising.

- Emollients and topical corticosteroids form the cornerstone in the management of atopic eczema.
- The appropriate and continued use of emollients may reduce the need for topical steroids by up to 50%, although the range of products available adds to the confusion and patient preference is often the key to success.
- Unfortunately, the lack of good quality evidence on the timing and order of application of topical products leads to conflicting advice and potentially poor concordance with treatment.

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Tables and Figures.

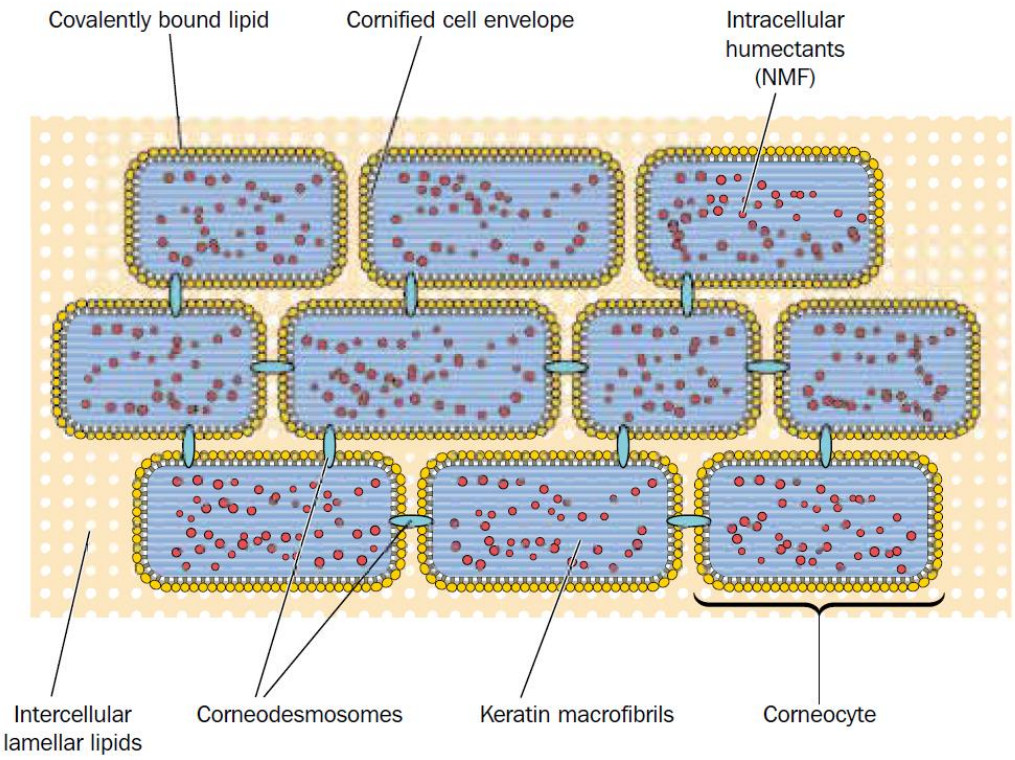

Figure 1: 'Bricks and Mortar' model of the stratum corneum (taken from Voegeli D, The vital role of emollients in the treatment of eczema. *British Journal of Nursing*, 2011, Vol 20, No 1 p9).

Beeswax
Benzyl alcohol
Butylated hydroxyanisole
Butylated hydroxytoluene
Cetostearyl alcohol (including cetyl and stearyl alcohol)
Chlorocresol
Edetic acid (EDTA)
Ethylenediamine
Fragrances
Hydroxybenzoates (parabens)
Imidurea
Isopropyl palmitate
N-(3-Chloroallyl)hexaminium chloride (quaternium 15)
Polysorbates
Propylene glycol
Sodium metabisulphite
Sorbic acid
Wool fat and related substances including lanolin

Table 1: Potential sensitizers found in emollients.

Although not common, reactions to emollient additives have been reported. This table lists the large number of additives found in some emollients, and these should be noted especially when a patient has a known allergy to any one of these. (BNF 72, 2016).

Source of recommendation:	Date:	steroid before emollient	Emollient before steroid	Time interval between topical treatments (mins)
National Prescribing Centre (NPC)	1998	X		NR
NPC	1999		X	10 – 20
Flohr & Williams	2004	X		60
National Eczema Society (NES)	2004	NR	NR	15
PRODIGY	2004	NR	NR	30
PRODIGY	2005	X		30
BNF	2004	NR	NR	30
BNF	2005	X		NR
Gradwell and McGarvey	2006	X		30
Hicklin	2006		X	30
Primary Care Dermatology Society (PCDS) and BAD	2006	X		30
NES	2008	NR	NR	15
NICE 2010	2010	X		NR
Knott	2012		X	10 – 15
Lawton	2013		X	NR
NES	2013	NR	NR	30
PCDS	2013		X	20
BNF; BNFC	2014 - 2016	NR	NR	“several”

Table 2. Summary of the recommendations concerning the order of application (steroid or emollient first) and recommended time intervals between applications (adapted from Smoker & Voegeli, 2014).

NR = No recommendation