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H₁-Antihistamines and itch in atopic dermatitis

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H₁-Antihistamines, especially the sedating type, have long been prescribed in atopic dermatitis (AD) in an attempt to reduce pruritus, the most important symptom with a major impact on health-related quality of life (1). However, a recent Cochrane systematic review (2) concluded that there is no reliable high-level evidence to support the use of these drugs in AD, particularly as a monotherapy. This conclusion was reached because the authors could find no randomised trials comparing an oral H₁-antihistamine with placebo or control. While this is true, evidence of other types, including the paper of Yamanaka and colleagues in this issue of Experimental Dermatology (3), is accumulating to support the view that H₁-antihistamines may be effective in relieving the itch associated with AD.

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From early studies with first generation H₁-antihistamines that had both peripheral and central effects, it was not possible to determine how their beneficial effects against itching in AD were produced. In fact many physicians believed that it was the sedative effect of antihistamines in promoting sleep and thereby reducing nocturnal scratching that was most important (4). A similar view is held by many clinicians treating chronic urticaria who believe that the addition of a night-time dose of a sedative antihistamine, such as hydroxyzine, is necessary for a restful night's sleep (5). What is generally not realised, however, is that old sedating antihistamines have detrimental effects on the quality of sleep, including reducing rapid eye movement (REM)-sleep (6). Furthermore, the long half-lives of these drugs mean that their somnolent effects persist well into the following day, resulting amongst other things in impaired learning in children and reduced work efficiency in adults (6).

The observations that minimally sedating second generation H₁-antihistamines were at least as effective in AD suggested a peripheral effect on H₁-receptors in the skin rather than a central effect, but definitive proof was lacking. This has now been obtained by the study of Yamanaka and colleagues (3) who showed that a second-generation H₁-antihistamine has beneficial effects in itch and scratching behaviour in AD patients without affecting sleep quality. A similar conclusion may be reached from a recent study in urticaria (5) in which the addition of a night-time dose of a sedating antihistamine had no additional effect compared to regular therapy with a non-sedating antihistamine on decreasing symptoms and night-time sleep disturbances and increasing quality of life. However, it significantly increased somnolence the following day, an unwanted effect.

So, if H₁-antihistamines act peripherally to reduce itch in AD, what are their possible mechanisms?

First, while the role of histamine in producing the symptoms of urticaria is well established, its participation in AD is more controversial. In their assessment of this topic, Buddenkotte and colleagues (1) reported that while early studies found elevated levels of histamine and numbers of dermal mast cells in AD patients, more recent evidence has not supported a role for histamine in AD. But are elevated levels of histamine necessary for H₁-antihistamines to have beneficial effects. The answer to this is no. H₁-antihistamines are not antagonists of the binding of histamine to H₁-receptors but are inverse agonists (7). As such, they bind to a different site on the receptor to stabilise it in the inactive state. Increased constitutive activity (i.e. increased activity in the absence of stimulation by an agonist) of many G-protein coupled receptors, including histamine H₁-receptors (7), has been demonstrated but it has not been studied in AD. Certainly, increased histamine H₁-receptor constitutive activity in AD would provide an excellent target for H₁-antihistamines in this condition.

While inflammatory mediators, such as histamine, are usually considered in isolation, in clinical disease a cocktail of mediators and cytokines is released into the extravascular space. These have the potential of interacting to produce additive effects. One potential interaction in AD involves bradykinin. Bradykinin, which evokes only weak itch and pain of similar intensities in non-lesional skin of patients with AD and in healthy volunteers, induces intense itch in lesional skin (8). Interestingly, H₁-antihistamines also inhibit bradykinin responses suggesting a co-operation between the histamine H₁-receptor and the bradykinin B₂-receptor (9).

A third possible mechanism involves the anti-inflammatory effects of H₁-antihistamines. H₁-antihistamines have the ability to down-regulate NF-kappaB, a ubiquitous transcription factor which promotes the production of a number of pro-inflammatory cytokines and adhesion proteins (7). However, an anti-inflammatory effect is unlikely to be responsible for the relatively rapid effects seen in the study of Yamanaka and colleagues (3).

In conclusion, the study of Yamanaka and colleagues (3) has confirmed the beneficial effects of a non-sedating second-generation H₁-antihistamine on itch and scratching behaviour in AD patients without affecting sleep quality. The clinical implications of this are two-fold; first, it re-enforces the potential of non-sedating second-generation H₁-antihistamines as an adjunct to AD therapy; and, second, it shows that central sedation is unnecessary for their activity and, consequently, sedative antihistamines should not be used because of their unwanted effects.

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