RAPPORT FINAL

HYDROxyzINE VERSUS CETirizINE IN THE TREATMENT OF

ATOPIC DERMATITIS IN CHILDREN

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SUMMARY

Twenty children suffering from atopic dermatitis have been enrolled in a 4-week double-blind, parallel, randomized study to assess the effectiveness of hydroxyzine 0.6 mg/kg bid versus cetirizine 0.2 mg/kg bid. Hydroxyzine appears to significantly improve redness, erythema, lichenification and total symptom severity score and to be significantly superior over cetirizine regarding lichenification and total symptom severity scores. There is a trend for the improvement of erythema under cetirizine. A discussion on the relative anti-\(H_1\) potency of the drugs is made. Finally, the results are explained by the fact that hydroxyzine is a clearly sedating anti-\(H_1\), while cetirizine, its main metabolite, belongs to the class of the non-sedating anti-\(H_1\). This first study has to be confirmed.
INTRODUCTION

Atopic dermatitis (AD) is a common condition [1] of multifactorial origin [2]. It is identified by a constellation of symptoms [3]. In infant and in children, these symptoms mainly consist in pruritus, skin lesions of face and extensors, chronic evolution and personal or family history of atopy [3]. Pruritus is the main symptom which provokes AD. Due to more scratching "distress associated with AD may lead to more symptoms" [4]. The disease is difficult to treat [5] and patients suffering from it "fill a large share of pediatric dermatology clinics" [5]. First-step treatment consists in avoiding external factors likely to provoke or perpetuate symptoms. This notably requires occupational and psychological guidance as well as rehydration of skin [5, 6]. In case of food allergy elimination diet improves the disease [7]. In case of failure and as a second step topical corticosteroid are useful [8]. However, besides these therapeutic strategies the control of pruritus is mandatory in children afflicted by AD and anti-H₁ can be administered for this purpose [5, 9]. The effect of antihistamines may be related to the possible release of histamine by mast cells in the course of AD [5]. It could also simply be due to the "soporific effects" of antihistamines [10, 11]. Hydroxyzine [1, 5, 9, 10, 12, 13, 14, 15] and diphenhydramine [5, 9] have been suggested or tested as antihistamines in the management of AD. In the recent years, non sedating anti-H₁ have also been tested in order to avoid the reduction of attention in school children due to older antihistamines. Results are not yet completely convincing [11, 15]. Cetirizine is an hydroxymetabolite of hydroxyzine producing "significant antihistaminic effect without the CNS changes [of hydroxyzine]" [16]. This characteristic led us to perform the present trial aimed at assessing for the first time the effect of cetirizine in AD in children by comparing in a double-blind manner the new generation anti-histamine cetirizine with its sedating parent compound, hydroxyzine.
MATERIALS AND METHODS

Study design

Double-blind, parallel, randomized, 4-week study consisting of an initial visit, an interim phone call at mid-trial and a final visit.

Patients

Twenty 2 to 12 years old children had to complete the study. They were suffering from AD according to the diagnostic criteria by HANIFIN J.M. and RAJKA D. [3] and needed an oral antihistamine treatment. Parents gave their consent after being completely informed about the studied drugs and protocol. Exclusion criteria were: severe atopic dermatitis requiring systemic drugs other than antihistamine, local or general infection, known allergy to piperazine, any disease or treatment likely to interfere with the trial, recent modification in diet, housing environment or contact with animals, renal or hepatic insufficiency and glaucoma.

Drugs

Hydroxyzine (p-chlorodiphenylmethyl-1(hydroxy-2-ethoxyethyl)-4 piperazine - ATARAX\textsuperscript{R}) and cetirizine ([2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl] ethoxy]acetic acid dihydrochloride - ZYRTEC\textsuperscript{R}), in droplet form (20 drops = 1 ml) were presented in identical and indistinguishable bottles of 100 ml at the concentrations of respectively 15 mg/ml and 5 mg/ml. Taste and aspect were exactly identical. Dosage was 0.6 mg/kg bid for hydroxyzine and 0.2 mg/kg bid for cetirizine. In case of severe lesions, use of fluocortin butyl (a very low potency topical steroid) was allowed.

CLINICAL EVALUATION

Clinical history

Complete history including demographic data were obtained at the initial visit. Previous treatments and outcomes of atopic dermatitis were recorded. Concomitant treatments were mentioned as well as age, sex and weight.
Investigator's evaluation

The evaluations were made both during the selection and conclusion visits. They consisted in filling in a classical draw and scale of both the front and the back sides of the concerned patient. Each side was separated into 10 areas. For each area investigator has to assess from 0 to 3 (0 = absence; 1 = slight, 2 = mild; 3 = serious) four symptoms: erythema, vesicles, excoriation and lichenification. At the final visit, the investigator has to indicate if, in his opinion, the improvement was due to the test-therapy or to the local therapy used.

Patient's evaluation

Patients, or their parents, were given a self-assessment card at the initial visit and were asked to fill it out every day to assess from 0 to 3: daytime pruritus, sleep troubles due to nighttime pruritus, redness, scratching lesions, excoriation and side-effects. At the final visit, the patient or his parents gave their opinion as to the improvement being the result of the test-therapy or of the local therapy. For analysis scores from day 1 to day 3 were compared to scores of the last 3 days.

COMPLIANCE

To check the drug compliance, a urine sample was collected at the last visit. Urines were immediately frozen and kept at -18°C to be analyzed later on at the UCB Laboratory of Drug Metabolism by HPLC method [17].

STATISTICAL ANALYSIS

Comparisons of the results of the initial visit and total symptom score by the parents were analyzed by the way of analysis of variance with one factor. Other comparisons were made by a multivariated analysis of variance with repeated measurements and two factors.
RESULTS

Twenty-four patients have been enrolled. Four of them dropped out. This was not linked to the trial. Of the remaining 20 patients, 9 belonged to the cetirizine group (C) and 11 to the hydroxyzine one (H). Twelve samples of urines have been collected and were all positive for cetirizine or hydroxyzine. No terfenadine metabolite was found. Improvement, if any, was always thought to be due to the test therapy as local therapy use was minute (2 patients, both in C-group).

Sex/age

The male/female ratio was 6/3 for C and 5/6 for H. Mean ages were respectively (years ± sd) 2.1 ± 0.3 and 4.0 ± 3.0.

Investigator’s assessment (see table I)

At the initial visit mean scores for redness, vesicles, erythema, lichenification and total symptom severity were not statistically different between C and H groups. After treatment we could only find a trend regarding pre-treatment score in the C group as far as the erythema was concerned. Conversely H improved significantly the redness, the erythema, the lichenification and the total symptom severity score, while only a trend was observed for the vesicles. Differences between C and H after treatment were significantly in favour of H for the lichenification and the total symptom severity score. Poor result of C is due to 2 therapeutic failures while all H-patients were clearly improved.

Patient (or parent)’s assessment (see table II)

A trend is observed for the daytime pruritus under H. For the redness, a significant improvement is observed under H and a trend under C. Other comparisons are not significant.
Side-effects

Both drugs were remarkably well tolerated. One patient complained of decrease in appetite for 3 days under C. This is very unlikely to be linked to the treatment.

DISCUSSION

Present study shows the superiority of hydroxyzine regarding cetirizine, its main metabolite, for the treatment of AD in children. The difference is mainly marked on investigator's total symptom severity score. Compliance was good. Checking the compliance is in our opinion a necessary step, especially in children afflicted by AD as the disease is often accompanied by difficulty in adhering to treatment prescriptions [4]. In the present study, compliance was doubtful in two cases but urine analyses were positive for both. From the literature cetirizine exhibits the same anti-H₄ activity than hydroxyzine without the CNS changes [16]. This good tolerance has generally been confirmed in pharmacoclinics [18, 19, 20] and in clinics [21, 22]. From these pharmacoclinical results, a study of SEIDEL W et al [23] showing that hydroxyzine impaired significantly more the multiple sleep test latency than cetirizine or placebo, is of course very relevant. Put together with the results of the present study, this strengthens the idea that anti H₁ of the sedating class such as hydroxyzine are more useful in the management of AD than anti H₁ of the non-sedating class such as cetirizine.

Of course, this is only proved if actually equipotent anti-H₁ dose of drugs are used. This equipotency should notably be shown by the classic method of the inhibition of the histamine-induced wheal and flare. Unfortunately, such studies comparing hydroxyzine and cetirizine do not exist in children and we had to chose the doses on indirect data. Recent publications tend to prove that the doses were properly chosen in the present study. On the one hand, WATSONS W.T.A. et al, [24] found in 19 children from 5-12 years, a significant inhibition of the histamine-induced wheals and flares from 0.5 h to 24 h after single intake of 0.18 mg/kg or 0.41 mg/kg cetirizine. On the other hand, SIMONS F.E.R. et al [14] found in 12 children 0.7 mg/kg hydroxyzine single intake to be clearly effective in relieving pruritus in AD for 2 to 24 hours. They underline the lack of advantage in twofolding the dose.
Pruritus is a major symptom eliciting skin lesions in AD. Indeed, in 1936, ENGMAEN W F et al showed that typical lesions of AD could be prevented when part of the skin was protected by a bandage avoiding scratching [25]. Pruritus can be provoked by many factors such as food allergens (7), aero allergens [27], but also psychological factors [4]. Psychological factor can even in itself provoke skin reactions: HANIFIN J M et al [10] quotes a 1953's paper where stressful experimental interviews induced measurable erythema leading to itching and scratching [27]. The importance of psychological factor is confirmed in a recent paper of KAREM M. and SAMPSON H.A. [4] who stated that "stress does appear to be an important predictor of AD symptoms in children". Finally, a pruritic disease such as AD can lead in itself to "anxiety" [5]. The fact that, in the present study hydroxyzine is superior to cetirizine in treating AD, while the difference in humans between the two drugs is their impact on CNS [16], reinforces the idea that psychological factors play (among others) an important role in provoking or perpetuating AD. This confirms the results of ROBERTS J et al [13] who found the non-sedating antihistamine astemizole to be less effective than hydroxyzine in the treatment of AD in children while in [9] dexchlorpheniramine (a sedating anti-H₁) was as effective as hydroxyzine (but the effect was not very marked in this study). Conversely, it is noteworthy that the only comparative study on cetirizine vs hydroxyzine in another dermatologic disease, chronic idiopathic urticaria, where psychological factors are usually thought to play a less prominent role than in AD, show that both drugs are equally effective (with less sedating effect for cetirizine [28]). This study was conducted in adults. It goes the same way than the very recent O. HAGERMARK'S statement that administration of antihistamines in chronic idiopathic urticaria "usually diminishes or removes the itch" while "new non-sedative H₁-receptor antagonists do not alleviate the itching in AD" [11].

However, we can speculate on the basis of our experience that the pruritus which afflicts children with AD is much more pronounced than pruritus in chronic idiopathic urticaria. This, of course, could be the explanation for the differences in results as hydroxyzine could not only act on stress or anxiety but also by preventing scratching by the patients (together with the anti-H₁ effect similar to the one of cetirizine).
As a conclusion, in the present trial, hydroxyzine appears to be superior to cetirizine in the treatment of AD in children. If doses were accurately chosen, these results reinforce the idea that psychological factors play a prominent role in provoking or perpetuating AD. This also strengthens the usefulness of hydroxyzine in stress and the fact that cetirizine belongs to the class of the non-sedating anti-H₁.

Present results, as they are the first concerning cetirizine in AD, need to be confirmed in larger series.
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