

Antihistamines in atopic dermatitis

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Atopic dermatitis (AD) is a chronic cutaneous disease characterized by its association with atopy: an elevated serum IgE level with high specific IgE to a number of common allergens (both inhalant and alimentary) is found in AD and there frequently occurs a personal or family history of allergic respiratory disease.

AD is a complex syndrome where adverse reactions to foods may play a pathogenetical role. However, adverse reactions to foods are only one of the possible causes of AD.

In the therapeutic management of AD, several possible approaches (single or combined) have to be considered. Physical treatment, preventive drugs, steroids, elimination diets, environmental controls, etc. are the most common tools employed in the treatment of AD. Antihistamines also are considered a useful tool in the treatment of AD and adverse reactions to foods, mainly for the control of such symptoms as itching (1).

In the following paper, we consider the more efficacious antihistaminic drugs available and future prospects in this field.

Histamine exerts its physiological effects through three different receptors: H1, H2 and H3. Pharmacological research has developed antihistaminic drugs of two classes: anti-H1 receptor blockers and anti-H2 receptor blockers. Anti-H1 receptor drugs are used widely for itching, which is mediated by H1 receptors.

Nevertheless, anti-H1 drugs have various side effects such as anticholinergic properties which can stimulate or depress the central nervous system resulting in symptoms such as agitation, restlessness, or more commonly drowsiness. In fact, drowsiness appears to be the major side effect limiting the usefulness of anti-

H1 drugs in the treatment of allergic patients. A new generation (the third) of anti-H1 drugs is now available.

As a group they lack any direct chemical relationship to histamine, but have as a common structure an aromatic nitrogen in the form of a piperidine, piazine, or pyridine. Furthermore, these structures are more polar and so their access to the central nervous system is limited, thereby reducing side effects. In paediatric patients the sedative effect of anti-H1 drugs may be considered a useful feature, whereas the opposite happens in adult patients.

Only recently a rationale has been reported for the use of both anti-H1 and anti-H2 compounds in adverse reactions to foods. Barret & Metcalfe (2) proposed that antihistamines may be effective in restoring the correct permeability of the enteric mucosa, thus reducing the passage of macromolecules.

The clinical experience with monotherapy of antihistamines have not been very impressive. In fact, Businco et al. (1) stated that "the specific effect of antihistamines is probably of no value" in the treatment of AD. We have previously reported that "anti-H1 antihistaminic drugs have poor clinical efficacy" in cutaneous disorders "due to adverse reactions to foods" (3). In addition, we reported that the combination of anti-H2 and anti-H1 compounds was no more effective than anti-H1 compounds alone (see Table 1.).

To confirm the clinical results, we recently designed a double-blind study to compare the clinical efficacy of ketotifen to oxatomide in the treatment of adverse reactions to foods. As reported in Table 1, no difference was detected between the efficacy of the two compounds (4).

Table 1

Clinical efficacy of different protocols in the treatment of urticaria-angioedema syndrome due to adverse reactions to food. Previously reported (3)

Placebo	20%
Terfenadine	29%
Astemizole	31%
Oxatomide	32%
Ketotifen	33%
Ranitidine + anti-H1	35%
Famotidine + anti-H1	37%

Results are expressed as percentages of clinical improvement.

These findings prompted us to try a new approach to adverse reactions to foods: we obtained better clinical results treating these pathological conditions with "cytoprotective" drugs (5).

However, side effects of each compound given to patients must be evaluated. The role of anti-allergic drugs on the immune system is not fully known. This clinical question, which has been extensively reviewed by our group in a recent paper (6), arose when it has been reported that several antibacterial compounds inhibited some functions of the immune response (7). We first investigated cromolyn, usually considered a molecule devoid of almost any side effects. Surprisingly we found cromolyn capable of exerting an enhancing effect on T cell proliferation (8). Briefly, several drugs have been studied and the protocol of investigation included T cell proliferation of peripheral blood lymphocytes and T cell clones, and the generation of lymphokines (mainly IL-2 and gamma-IFN

production). T cell activation has been investigated with five different activating stimuli:

- Phytohemagglutinin, a common mitogen of T cells;
- AMLR (autologous mixed lymphocyte reaction), defective in AD (9) and in respiratory allergy (10);
- Through the CD3/TCR (T cell receptor for the antigen) complex, through the CD2 complex
- Through the CD28 molecular structure.

Some of these *in vitro* findings have been supported by *in vivo* results (6).

In Table 2, the results of our experiments are summarized. The compounds are defined as "Inert", including almost all the anti-H1 drugs, with no effect on the immune response; as "Enhancing", cromolyn, the only drug increasing the T cell proliferation (probably enhancing IL-2 receptor expression); and "Depression" several compounds, such as ketotifen, anti-H2 and glucocorticosteroids, with a negative effect on the immune response.

Some conclusions are suggested from these experiments:

- Anti-H1 monotherapy alone is not suggested.
- The clinical use of anti-H1 should be directed at the symptoms.
- In the absence of side effects, anti-H1 drugs (mainly the new generations), may be considered to be useful tools in association with other etiopathogenetical treatments.

Table 2

Anti-allergic drugs and the immune response

Enhancing	Inert	Depressing
Cromoglycate	Oxatomide	Ketotifen
	Astemizole	Cimetidine
	Levocabastine	Ranitidine
	Fenoterol	Glucocorticosteroids
	Pirenzepine	
	Rosaprostol	

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