

Pharmacological influence of antiallergic medication on *in vivo* allergen testing

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Background

The allergen skin test has become one of the fundamental ingredients of the clinical allergy work-up. A question frequently encountered is which of our common pharmacological agents used for treating allergic disease has an influence on the results of the skin tests. The questions regarding pharmacological influence are often extended to the influence on other target organs of local provocation, such as the nose, conjunctiva and bronchus. Which agents should be avoided before tests? How long should the agents be avoided before testing in order to be sure that a valid result is obtained? This review will deal with the major groups of therapeutic agents currently used for allergic diseases and asthma. The review is not intended to be complete in all details, but rather to provide some basis for simple guide-lines in the practical clinical management.

One should be aware that the effects of these agents are mostly inhibitory; this means that we might obtain false negative results from an allergen test under the influence of a pharmacological agent. However, this also means that a positive result should be regarded as a valid result. Whether drugs used for the treatment of other diseases, such as cytostatic drugs, influence the responsiveness of the target

organs, thereby creating false negative results, may be suspected on direct evidence. However, little or no information about other drug effects on histamine and allergen-induced reactions are available and is not the subject of the present review.

It is also important to note in this context, when dealing with the challenge of different target organs, the presence of allergen-increased responsiveness (2, 12, 13). This is a phenomenon which in the nose has been called "priming". Thus, a challenge of a specific target organ increases the response to a re-challenge of the same organ within the next couple of days. This phenomenon is not specific, and means that an increased responsiveness is also obtained to unspecific agents, such as histamine and metacholine (12). In consequence, at least a week should elapse between active challenges of the same target organ, whether it is nose, conjunctiva or bronchus. This phenomenon also appears to exist during natural allergen exposure, as patients with hay fever increase their responsiveness during the pollen season (7, 24). It is also interesting to note that this appears to be a phenomenon of airway mucosa only, as it does not occur in the human skin (4). The explanation of this apparent contradiction between airway mucosa and skin is still unclear.

Antihistamines

Since their introduction in the 1940's, antihistamines have become one of the main therapeutic agents in allergy treatment (29). They are mainly used as oral medication for systemic treatment, although topical preparations are used for the local treatment of allergic ocular symptoms. One of the reasons why these preparations are not used topically to a greater extent, is that they are suspected of producing local sensitization. Their widespread use as eye drops should disperse these fears, and newer antihistamines, such as levocabastine, are now being tested as topical preparations for nasal use as well.

Orally administered antihistamines, H_1 antagonists, have been shown to reduce the weal and flare response of skin tests, as well as other local provocations in the nose and conjunctiva (17, 18, 21, 22). It has also been shown that high doses of antihistamines have an effect on bronchial allergen challenge testing, although this appears to be minimal when normal doses are used (31). The duration of the inhibitory effect appears to be coupled with the human half-life of the substance. Consequently, most of the current antihistamines should be discontinued 2-3 days before any antigen challenge, whether dermal or otherwise. In this respect the newer antihistamines, like terfenadine and levocabastine, have properties similar to the older ones, while astemizole with its very long half-life should be discontinued 6-8 weeks before actual challenge (20). Although there are indications that H_2 blockers might contribute to an inhibitory effect of H_1 blockers there is at present no data showing that patients should be taken off these as well. Topically applied antihistamines are absorbed through the mucosa and found in the systemic circulation (31). However, the actual concentration obtained appears to be so low that they must be considered to lack any inhibitory effect outside the actual target dose.

Recommendations: Oral antihistamines should be discontinued 2-3 days before and astemizole 6-8 weeks before any challenge regardless of the

target organ. Topical antihistamines, especially the ocular, should be discontinued in the intended challenge organ 2-3 days before challenge.

Glucocorticosteroids

The general notion has been that glucocorticoids lack any inhibitory effect on the immediate allergen challenge, but have an inhibitory effect on any late phase allergic reaction (36). The principal basis for the notion has been studies using fairly short oral dosage of glucocorticosteroids (30, 39). These findings appear to be supported by *in vitro* data using isolated basophils and lung mast cells (37, 38). However, evidence is now accumulating which suggests that potent glucocorticoids applied topically for extended periods actually inhibit the immediate allergic reactions, as well as non-specific hyperreactivity, regardless of whether the application is dermal, nasal or bronchial (3, 10, 14, 15, 35, 43, 47). Although data from ocular challenges is lacking at present, it appears likely that the same phenomenon occurs at this site also. As the clinical use of topical glucocorticoids is increasing and they are rapidly becoming a first-choice in the treatment of continuous allergic diseases, these findings are increasingly important. The effect on the immediate allergic reaction appears to be dependent on the amount applied directly to the target organ and the strength of the preparation, thus the risk of affecting the immediate allergic reaction in another organ would appear minimal. The duration of an anti-allergic effect after discontinuing the therapy is not fully clarified. However, it appears likely that no effect is present after 2-3 weeks.

Recommendations: Regardless of the location of challenge, it is not necessary to discontinue low dose oral glucocorticosteroids (< 10-15 mg of prednisolone/day). High dose glucocorticosteroids should be reduced, if possible, to the dose level above. Topical steroids should be discontinued in the challenge site 2-3 weeks before challenge, whether the site is the skin, nose, bronchi or eyes. As the patients may be dependent on glucocorticoid therapy for their

well-being, certain steps should be taken. Whatever the challenge procedure, if patients cannot be without their glucocorticoids and if the effects of the treatment are only to be followed over time, it is important to maintain the same constant steroid dose 2–3 weeks before challenge.

Disodium cromoglycate

Locally administered disodium cromoglycate (DSCG) has been shown to have a protective effect when it comes to allergen challenge on mucous membranes such as bronchial, nasal and ocular, but not the skin (1, 23, 34). This discrepancy may point to some interesting pharmacological differences between the mast cells in the skin and mucous membranes, but could also be dependent on differences in the local uptake of the substance. It appears that the effect is wholly dependent on the topical mode of administration, and the risk of affecting other sites is minimal. The duration of the effect appears to be short. The question of whether any long-term shift in baseline might be the result of long-term treatment, as has been suggested, is still open.

Recommendations: Locally applied substance in the target organ in question should be discontinued 12–24 h before challenge.

Beta₂-adrenostimulants

Apart from the well-known effects on smooth muscle and other muscular tissues, β_2 -adrenostimulants have been shown to possess several other properties, e.g. they can inhibit induced mediator release from mediator cells and also inhibit microvascular leakage induced by potent peptides such as bradykinins (27, 44). Thus, there is a theoretical basis for the notion that these agents should also be able to influence allergen-induced reactions where there are no smooth muscles such as the skin, nose and conjunctiva. Although not completely without contradictions there are reports that systemically applied β_2 -adrenostimulants can influence skin tests (11, 19, 41). The results are more

conclusive when the β_2 -adrenostimulants are given topically. Thus, the reactions in bronchi, nose and skin are inhibited, although these modes of administration are not used in the clinical situation (19, 42, 45, 46). It is also reasonable to believe that they might inhibit local conjunctival reactions even if this is not the best way of administering these drugs at present. The duration of these effects appears to depend on the plasma half-life of the substances. Moreover, although a bronchially applied substance is absorbed through the bronchial mucosa the plasma levels achieved are generally so low that the risk of influencing other potential target organs must be considered minimal.

Recommendations: Oral β_2 -adrenostimulants should be discontinued 12–18 h before provocation, the timing dependent on the half-life of the substance. 12 h appears sufficient for salbutamol and terbutaline. The longer time of 18 h applies to fenoterol. Bronchially applied drugs do not need to be suspended if a challenge in another site is intended. In such cases the same time interval as above should apply.

Xanthin preparations

The effect of theophylline on the most common *in vivo* allergen challenge test, the skin test, appears somewhat variable. The effect has been described as suppressive, negligible or variable (11, 16, 17, 42). Variations in the plasma levels of theophyllines do not appear to be the only explanation for these variable results. With bronchial provocation testing, the results appear more conclusive, as theophylline seems to have a protective effect (40). There is also a recent report that oral theophylline has a protective effect on nasal allergen provocation testing (26). There have been no reports on the effect of theophylline on conjunctival provocation.

Recommendation: Theophyllines, administered orally, should be withheld for 24 h prior to challenge. Sustained-release preparations should be discontinued for 48 h.

Alpha-agonists

Alpha-adrenergic drugs have been replaced by β_2 -adrenergic drugs for the treatment of the lower airways. However, α -agonists are widely used for the treatment of inflammatory oedema in the upper airways and conjunctiva, regardless of the pathogenesis (5, 6, 8). The effect of these drugs is mainly an increase in vascular tone. In the nose, their principal target are capacitance vessels, since they are responsible for the regulation of nasal patency. In the lower airways the mucosal component has lesser significance than the smooth muscle component in the regulation of airflow. This mode of treatment therefore appears of minor importance. Thus, the α -agonists are supplied as topical preparations, for ocular and nasal use. They are also supplied as oral decongestant preparations, such as pseudoephedrine and phenylpropanolamines. When applied locally the substances have a negative influence on allergen- and histamine-induced reactions in the nose and probably in the eyes. This also appears to be the result of the oral medications. However, at present there are no studies which show that α -agonists should be able to protect the lower airways and the skin in a challenge situation, although this should be theoretically possible if a high enough dose is given.

Recommendations: Locally applied α -agonists are withheld for 24 h before challenge in the relevant provocation target. From a theoretical point of view, this time limit should also be valid for orally applied substances, and tests in other organs such as the bronchi and skin.

Anticholinergics

During the last couple of years a new anticholinergic drug, ipratropium bromide, has been developed for asthma therapy (28). The same drug has also been used for treating patients with excess secretions as a component of non-allergic perennial rhinitis (25). The topical mode of administration was then used in the nose as well. There is at present no data indicating that this drug given in one site should be

able to affect antigen-induced reactions in another. It has been suggested that a topically applied substance in the bronchi mainly changes the basal tonus but not the reactivity *per se*. Thus, the reaction to antigen should be unaffected. As yet this has not been clarified.

Recommendations: Topically applied substances, should be discontinued 24 h before provocation in the organ in question.

Ketotifen

An antihistaminic substance claimed to possess mast cell stabilizing effects as well. This drug is widely used, particularly in South East Asia. It is given as an oral preparation. As it is able to influence antigen-induced reactions, it must be considered to possess the same properties as antihistamines and should be handled accordingly.

Recommendations: It should be discontinued 48 h before testing.

Conclusion

Almost all drugs used in the treatment of allergic airway disease can influence the results of an *in vivo* allergen challenge. However, it should be kept in mind that the effects are inhibitory; this means that a positive result should be regarded as a true result, although it might be on a lower level than it would have been without the influence of drugs.

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