Institute for Experimental and Clinical Pharmacology and Toxicology[1], Friedrich-Alexander-University of Erlangen, Germany, Viatris GmbH[2], Frankfurt am Main, Germany, Department of Pharmaceutics[3], University of Florida, Gainesville, USA

Possibilities in improvement of glucocorticoid treatments in asthma with special reference to loteprednol etabonate

I. Szelenyi[1], R. Hermann[2], U. Petzold[2], A. Pahl[1], G. Hochhaus[3]

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Prof. Dr. I. Szelenyi, Institute for Experimental and Clinical Pharmacology and Toxicology Friedrich-Alexander-University of Erlangen, Fahrstr. 17, D-91054 Erlangen

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Allergic conditions contribute significantly to the burden of chronic disease in the industrialized world. The increasing prevalence has lead research into the discovery and development of various new therapeutic strategies. Despite considerable efforts of the pharmaceutical industry, the leukotriene antagonists were the only new class of asthma treatments to be licensed in the past 30 years. Topical glucocorticoids (GCs) are the most potent and effective therapy for treating allergic diseases. However, their use is limited by diverse undesired effects. Changes in pharmacokinetic parameters of GCs may be an interesting and promising approach to improve efficacy and safety of inhaled GCs. Loteprednol etabonate has been developed on the basis of the retrometabolic drug design. In animal studies, it has been demonstrated to have long-lasting anti-allergic (anti-asthmatic) effects without influencing the hypothalamic-pituitary axis (HPA). This soft steroid is now in phase III of the clinical development. Recently, loteprednol has been proven to be effective in the management of allergic rhinitis (400 μg once daily). No suppression of HPA was observed at clinically effective and higher doses. In conclusion, loteprednol as the first representative of soft steroids elicits marked anti-inflammatory effects, but has no impact on endocrine responses. It may represent a promising new therapy in the treatment of allergic rhinitis and asthma.

1. Introduction

Allergic disorders such as asthma bronchiale and rhinitis have emerged as a major public health problem worldwide over the past 20 years. Although data indicate that current therapies led to limited decreases in death rates, it continues to be a significant health care problem (Mannino et al. 2002). It still is one of the leading causes of preventable hospitalization worldwide and accounts for several million lost workdays. Along with the increase in the prevalence of allergic diseases, the costs associated with this disease have also risen dramatically (Tartasky 1999).

There is now strong evidence that airway inflammation is a predominant underlying problem in patients with rhinitis and/or asthma. The pathophysiology of allergic diseases involves an intricate network of molecular and cellular interactions, although the contribution of each individual factor is probably different from patient to patient depending on the setting and stimulus. Topical glucocorticoids (GCs) have become the mainstay of therapy in chronic allergic disorders. They are the clinically most effective treatment available but can produce serious secondary undesired effects.

Despite the long history and the documented efficacy of these drugs in controlling rhinitis and asthma, there are still concerns regarding the safety of these drugs in children, most specifically related to the potential for adrenal suppression and growth retardation. Since GCs administered topically may circulate systemically, a risk of growth suppression in children treated with these drugs cannot be ruled out. On the other hand, other adverse effects have been described. Prolonged exposure to topical corticosteroids among adults has been reported to increase cataract risk (Jick et al. 2001). There is also evidence that topical GCs can cause ocular hypertension or open angle glaucoma (Desnoeck et al. 2001). Therefore, there is still need to improve the present therapy with GCs.

2. Investigations, results and discussion

One of the hypothetical possibilities to improve the present GC therapy is to change certain pharmacokinetic parameters of the GCs. Such a promising approach takes the metabolic possibilities into account. In the early 80ies, Bodor developed an interesting concept (1980). Based on the retrometabolic design, he synthesized so-called soft-drugs, including steroids. The basis of his innovative concept is the use of an inactive metabolite that is than converted to an active derivative which is inactivated by a simple mechanism (e.g. splitting by esterases). The so-called soft-steroids such as loteprednol and etiprodnol belong to a new class of steroids. Loteprednol is the first representative of this new drug class synthesized by using the retrometabolic design (Bodor 1984; 1990; 1999). It has been approved for the treatment of conjunctivitis and uveitis in the United States (Howes 2000).

Table 1: Ratios between the lowest "side-effect-inducing" dose[1] and a moderately effective therapeutic dose[2]

Compounds	Ratios
Beclomethasone dipropionate	0.3
Budesonide	2
Fluticasone	2
Loteprednol etabonate	40

[1] The dose which causes a significant reduction of thymus weight in Brown Norway rats
[2] The dose which causes about 50–60% inhibition of airway eosinophilia in actively sensitized Brown Norway rats

2.1. Some new data on preclinical efficacy and safety of loteprednol etabonate

Loteprednol has intensively been investigated in animal models of allergic diseases. Recently, we have demonstrated that it effectively attenuates early and late phase allergic responses in animal models of asthma without influencing thymus weight and plasma cortisol levels in animals (Poppe et al. 1998; Szelenyi et al. 2000). Table 1 shows the ratios of intrapulmonal doses which induced moderate, about 60% inhibition of late phase eosinophilia in actively sensitized and challenged Brown Norway rats and those which caused significant reduction of the thymus following intrapulmonal drug administration on five consecutive days. As expected, beclomethasone (dipropionate) presented the most disadvantageous ratio. Both fluticasone and budesonide demonstrated favorable ratios of two indicating that there is a relatively good therapeutic ratio. However, these ratios were much lower than those obtained for loteprednol. Its ratio of 40 represents a remarkably favorable relationship between the therapeutically necessary airways eosinophilia inhibitory and the side-effect inducing doses (Poppe and Szelenyi, 1998). These results were later confirmed in domestic pigs. High doses of loteprednol (500–1000 μg/pig, about 50–100 μg/kg) given intranasally or intrapulmonally to anesthetized pigs resulted in measurable plasma levels. However, the plasma cortisol levels remained practically unchanged (Fig.).

2.2. Clinical safety and efficacy of loteprednol etabonate

Recently, the clinical development of loteprednol for intranasal use has been initiated. The effects on the 24 h plasma cortisol levels of intranasally administered loteprednol

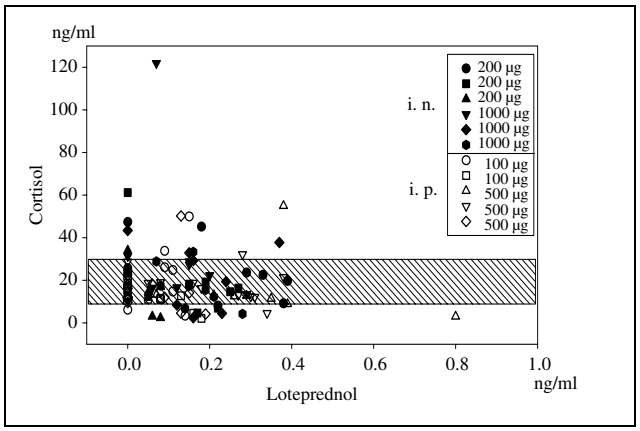

Fig.: The relationship between plasma loteprednol and cortisol level in anesthetized domestic pigs. 100–1000 μg/pig of loteprednol were given either intranasally or directly into the lung. The average body weight of domestic pigs amounted to 10 kg. Blood samples were taken from the V. jugularis every 60 min for 8 h. Plasma levels of loteprednol and cortisol were determined by HPLC

Table 2: Effects of loteprednol and fluticasone on the late phase eosinophilia in actively sensitized and challenged guinea pigs

	Doses in μg/kg given intratracheally	Remaining inhibitory activity observed after 6-h-pretreatment (inhibition of eosinophilia observed after 2-h-pretreatment with the compounds was equal to 100%)
Loteprednol	3.0	80
	10.0	71
	30.0	90
Fluticasone	0.5	51
	1.0	57
	3.0	53

Compounds were given 2 and 6 h prior to challenge, respectively. Numbers represent the extent of inhibition observed after 6-h-pretreatment in comparison to the 2-h-inhibition (100%)

was investigated in healthy male subjects. There was no significant suppression of the hypothalamic-pituitary axis at any loteprednol doses tested. Although not statistically significant, there was a trend for fluticasone to show 24 h cortisol suppression. When individual values were considered 3 of 8 subjects in the fluticasone-group showed distinct differences in the 24 h-cortisol pattern as compared to baseline (data on file, Prof. N. Bodor, Gainesville).

The clinical efficacy of loteprednol has been investigated in two clinical Phase II/III studies. In a pilot study, the efficacy of loteprednol was assessed in the treatment of seasonal allergic rhinitis induced by allergen challenge in an environmental exposure unit. The once daily 400 μg dose has proven to be effective in preventing the expression of symptoms of seasonal allergic rhinitis in adult patients (Geldmacher et al. 2002).

In a further, double-blind, placebo-controlled, randomized, parallel group study, the therapeutic efficacy of four doses of loteprednol containing nasal spray (100 μg, 200 μg, 400 μg and 800 μg) was investigated in the treatment of adults and adolescents with allergic rhinitis induced by grass pollen. Fluticasone (200 μg, Flonase®) was used as an open active-control. The aim of the study to assess the dose-related efficacy of loteprednol in allergic rhinitis and to evaluate its safety and tolerability. Loteprednol nasal spray was significantly effective in relieving the overall nasal symptoms of rhinitis at doses of 400 μg and 800 μg daily in patients suffering from seasonal allergic rhinitis. Its efficacy was comparable with that of fluticasone. The anti-allergic effect of loteprednol lasted 24 h indicating that loteprednol is a once daily drug. It was safe and well-tolerated in terms of adverse events reported and clinical and laboratory findings observed at all doses tested.

In summary, the preclinical data generated for loteprednol were successfully confirmed in the first clinical trials. Thus, loteprednol is a promising candidate for a safer GC therapy in allergic disorders.

3. Experimental

3.1. Determination of the ratio between ths lowest "side-effect-inducing" dose and a moderately effective therapeutic dose

Brown-Norway rats were actively sensitized with ovalbumin and *Bordetella pertussis*. Compounds were given as a dry powder intrapulmonally two hours prior to the allergen challenge. 48 h later, the animals were sacrified and a bronchoalveolar lavage (BAL) was performed. The total cell number and the number of eosinophils from the pooled BAL are counted using a haemocytometer (Technicon H1E). In a second series of experiments, animals were treated with the compounds intrapulmonally on 5 consecutive days. 24 h after the last admnistration, the thymus was removed and weighed (Poppe and Szelenyi, 1998).[4]

3.2. Effects of loteprednol and fluticasone on the late phase eosinophilia in actively sensitized and challenged guinea pigs

Male guinea-pigs are actively sensitized with i.p. injections of ovalbumin and aluminium hydroxide on two consecutive days. 14 days after the second injection the animals are used for experiments. Test compounds were administered as dry powder intrapulmonally following a tracheotomy two or six hours prior to allergen (ovalbumin) challenge. The animals are also treated with low doses of pyrilamine to prevent them from anaphylactic shock. Guinea pigs were sacrificed 24 h later. Afterwards, a BAL is performed with phosphate buffered saline. The total cell number and the number of eosinophils from the pooled BAL are counted using a haemocytometer (Technicon H1E; Poppe et al. 1998).[5]

[4] Data were partly presented at the XIIIth International Congress of Pharmacology, München, 26–31 July 1998.
[5] Data were presented in part at the annual meeting of the American Thoracic Society, Chicago, April 24–29, 1998.

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