

Current issues of basic and clinical glucocorticoid research

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Even today, over 50 years after their introduction into clinical medicine, glucocorticoids are the most effective anti-inflammatory and immunomodulatory drugs at our disposal. This statement even applies in the era of the biologics and COX 2-specific inhibitors. The glucocorticoids are therefore among the most important drugs used in routine clinical practice. In particular, optimal therapy in rheumatology would not be possible without this class of substances. Just imagine what it would be like without the possibilities of, for example, pulse therapy with methylprednisolone or prednisolone, if it were not possible to treat patients with low-dose glucocorticoid therapy or to apply glucocorticoids intra-articularly – our clinical success would certainly be distinctly limited compared with the status quo. On the other hand, glucocorticoids – especially in the case of incorrect application – are undoubtedly also drugs that have a high potential for side effects (Table I).

The incidence and intensity of side effects are especially dependent on the dose and duration of application. This knowledge underscores the duty placed on the attending physician to apply glucocorticoids responsibly and under regular and strict consideration of the benefit-risk ratio. The area of tension between high clinical efficacy on the one hand, and significant, only partially avoidable or treatable side effects on the other, is the reason why the glucocorticoids remain the subject of basic research and applied clinical research

Table I. Some of the possible side effects of low-dose glucocorticoid therapy.

Fat redistribution, weight gain, Cushing's syndrome
Altered water and electrolyte balance, hypertension
Osteoporosis
Disorders of glucose metabolism or diabetes
Myopathy
Suppression of the hypothalamus-pituitary-adrenocortical axis
Cataract, glaucoma
Peptic ulcer disease (in combination with non-steroidal drug therapy)
Psychological and behavioural disturbances

today. Attention is currently focused on three main problem areas:

1. Further research on the mechanisms of action.
2. Work on the development of glucocorticoids and glucocorticoid receptor ligands with an improved benefit-risk ratio.
3. Optimisation of the clinical application of currently available glucocorticoids.

The current situation concerning these three points will be outlined below.

Research on the mechanisms of action

Today it is clear that glucocorticoids mediate their main therapeutic effects via their genomic actions, i.e. via their receptors located in the cytosol (1). This mechanism has been thoroughly researched, although our detailed knowledge is constantly growing here, as well. In contrast, uncertainty remains regarding the two clinically relevant questions of how glucocorticoids achieve their very rapid effects and why high doses are disproportionately more effective than low doses. The existence of non-genomic actions is being discussed as an answer to these two questions (1). Unspecific non-genomic (i.e. mediated without direct, primary interaction with the genome) and specific non-genomic actions have been distinguished (1,2). The unspecific non-genomic actions – probably only occurring at very high doses (pulse therapy, intra-articular injections) – are therapeutically relevant physicochemical interactions with cellular membranes. The existence of membrane-bound receptors for mediation of the specific non-genomic actions is suspected. Intensive research is being conducted in this field, and a significant increase in findings is expected in the near future. More detailed literature is recommended for the interested reader (2, 3).

Development of new glucocorticoids and glucocorticoid receptor ligands

The association mentioned above between effect and side effects in the application of glucocorticoids has already generated a desire for the devel-

opment of optimised glucocorticoids at an early stage. This idea was initially discarded under the impression that the effects and side effects were inseparably linked. It was assumed that after binding of the glucocorticoid to its receptor, the activated glucocorticoid receptor complex induces both effects and side effects at the genome in a virtually undifferentiated manner. As greater knowledge was gained about the detailed mechanisms, this conception was increasingly shown to be incorrect.

A major milestone was then the discovery that the activated glucocorticoid receptor complex, beside its binding to glucocorticoid-responsive elements in the nucleus, also binds to transcription factors (activator protein 1, NFkB) and thus inhibits their action. In the subsequent period, more and more research results suggested that the anti-inflammatory properties of glucocorticoids are caused mostly by repression of the activator protein 1- and NFkB-stimulated synthesis of inflammatory mediators, whereas most of their adverse effects are associated with the transactivation of genes involved in metabolic processes (4). For this reason, researchers started to look for novel glucocorticoid receptor (GR) ligands that have high repression but low transactivation activities. Recently, a very promising substance was described – A276575 and its four enantiomers. Similarly to dexamethasone, it exhibits a high affinity for glucocorticoid receptors and potently represses IL 1 β -stimulated IL-6 production, but in contrast to dexamethasone it causes a smaller induction of aromatase activity (4). Accordingly, this clearly represents the first successful attempt to synthesise a novel, non-steroidal glucocorticoid receptor ligand that possesses high repression activities against inflammatory mediator production, but has lower GRE trans-activation activities than traditional steroids. We will have to follow this interesting development very attentively.

Optimisation of the clinical application of currently available glucocorticoids

A comprehensive response to the ques-

tion of how glucocorticoid therapy can be optimised with the drugs available would go beyond the scope of an editorial. Therefore, just two important aspects are mentioned here: 1) correct nomenclature and the application of the different dose ranges as indicated, and 2) knowledge of the existence, incidence, avoidability and treatability of glucocorticoid-induced osteoporosis. With regard to the first point, reference is made here to a recently published paper that deals in detail with the problem area mentioned and makes appropriate suggestions (5).

With regard to the second point, it is important to mention that glucocorticoids, prescribed for their anti-inflammatory and immunosuppressive properties, are the most common cause of secondary osteoporosis (6). The mechanisms of these adverse effects of the glucocorticoids are manifold and were recently described in reviews (7-9). It is estimated that glucocorticoid-induced osteoporosis occurs in around 50% of patients who have been on glucocorticoid therapy for more than 6 months (10, 11). At the same time, the question of a safe dose, in other words a glucocorticoid dose without clinically significant side effects on bone, remains unanswered. Thus, relevant side effects with regard to osteoporosis induction are also reported for 7.5 mg prednisolone equivalent per day (12, 13). The relative risk of vertebral fracture increases from 1.55 at < 2.5 mg per day to 5.18 in patients with > 7.5 mg per day (14).

In this issue of *Clinical and Experimental Rheumatology*, van Everdingen *et al.* report on a study in which 81 patients with early active rheumatoid arthritis (RA) received either 10 mg/d prednisone or placebo (in addition to NSAIDs, sulphasalazine, 500 mg calcium supplement) from 1992 – 1995 (15). The authors found numerically more lumbar vertebral spine fractures and a reduced bone density in the area of the lumbar spine, although the differences compared with the placebo group did not achieve statistical significance – probably due to the relatively small number of patients. Since the reduction in bone density (delta about

0.5 SD compared with placebo) of the lumbar spine only partially explained the increased incidence of fractures (this rate was doubled as compared with placebo, a finding which would be more compatible with a decrease of 1.0 SD), the authors conclude that low-dose prednisone therapy in patients with early active previously untreated RA not only increases the risk of fractures by reducing bone density, but also by changing bone strength and structure (15, 16).

This conclusion is supported by the identification of problems that occur in the use of bone density measurement for diagnostics and monitoring of the disease course in osteoporosis (6). For example, Peel *et al.* found that the incidence of fracture is higher in patients with glucocorticoid-induced osteoporosis than in those with postmeno-pausal or involutional osteoporosis, even though the bone mineral density is relatively higher in those patients (17). A high bone turnover as induced by glucocorticoid treatment is possibly responsible for disrupting the microarchitecture of bone (6). Unfortunately, parameters of bone microarchitecture are not recorded by the established methods for measuring bone density. On the other hand, this problem is well known, and several different research groups are involved in developing measuring methods to rectify the situation. Independently of this, however, the paper by van Everdingen *et al.* again shows the necessity: (i) to establish strict indications, as a matter of principle, for glucocorticoid therapy – even for low- and medium-dose regimens (5), and (ii) to conduct the diagnostics, prevention and therapy of glucocorticoid-induced osteoporosis consistently. The clinical importance of such action is underscored by the observation that fractures occur in roughly one-third of patients who are treated with glucocorticoids for more than one year (18,19). What is to be done in view of these impressive figures? Overall, an unequivocal standard for the prevention and therapy of glucocorticoid-induced osteoporosis is not available (20), but guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis

were issued by the American College of Rheumatology in 1996 (21) and updated in 2001 (22). Other examples are guidelines from the UK Consensus Group (23, 24). However, in a paper just published, Solomon *et al.* (25) report that the practical implementation of such guidelines is not very consistent. For example, bone density was measured in only 23% of patients with rheumatoid arthritis who were taking a mean daily dosage of 8.8 mg prednisone over 15 months, less than half of the patients were taking prescription medication for osteoporosis, and only one quarter were documented as taking calcium and/or vitamin D. The situation in Europe is probably similarly suboptimal. The dissemination of information on this subject will therefore be just as important as the analysis of actually achieved treatment quality in the future.

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