EXTENDED REPORT

Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology

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In rheumatology and other medical specialties there is a discrepancy between the widespread use and the imprecise designation of glucocorticoid treatment regimens. Verbal descriptions of glucocorticoid treatment regimens used in various phases of diseases vary between countries and institutions. Given this background, a workshop under the auspices of the EULAR Standing Committee on International Clinical Studies including Therapeutic Trials was held to discuss this issue and to seek a consensus on nomenclature for glucocorticoid treatment. This report summarises the panel's discussion and recognises that answers derived from consensus conferences are not definitive. Nevertheless, recommendations on glucocorticoid treatment are presented that (1) reflect current and best knowledge available and (2) take into account current clinical practice. A question-answer rationale presentation style has been chosen to convey the messages, to summarise the meeting in a readable format, and to avoid dogmatism.

Glucocorticoids have profound anti-inflammatory and immunosuppressive actions when used therapeutically. The therapeutic dose is very wide and depends on the indication for treatment, but can vary more than 200-fold. Clearly, different dosages and dosing regimens have distinct therapeutically relevant effects mediated by genomic and non-genomic actions. Genomic actions involve the binding to cytosolic glucocorticoid receptors, occur at any therapeutically relevant dosage, and are seen not earlier than 30 minutes after receptor binding. In contrast, non-genomic actions are mediated via biological membranes, and are seen at higher concentrations and within seconds or minutes (see below). However, the basis for the use of different dosages in different clinical conditions is essentially empirical as the evidence to support preferences in specific clinical settings is very scarce. This is aggravated by the discrepancy between the widespread use and the imprecise designation of glucocorticoid treatment regimens in rheumatology, as in other medical specialties. Nomenclature and terminology of glucocorticoid treatment regimens used in various indications and phases of diseases varies between countries and institutions. The current terminological confusion is exemplified by the different interpretations of the various terms used to describe dosage (very low, low, mild, mild to moderate, moderate, high, very high, ultra-high, and megadoses) and by the great variation in interpretation of the terms "low dose therapy", "high dose therapy", and "pulse therapy". A clarification of this situation is needed, firstly, for scientific conciseness in clinical terms to compare trials and, secondly, because glucocorticoid actions are strongly dose dependent in both a quantitative and qualitative manner.[1 2] Moreover, it should be noted that there is currently a renewed interest in glucocorticoids based on studies describing their disease modifying effects in rheumatoid arthritis.[3–5]

Given this background, a workshop was held to discuss this issue and to seek a consensus on nomenclature for glucocorticoid treatment. A panel of experts was convened under the auspices of the EULAR Standing Committee on International Clinical Studies including Therapeutic Trials. The panel comprised rheumatologists from Germany, the United Kingdom, Italy, Portugal, Switzerland and The Netherlands who met in Berlin on 7 April 2001 for the First European Workshop on Glucocorticoid Therapy. This report summarises the panel's discussion and recognises that answers derived from consensus conferences are not definitive. Nevertheless, we present recommendations on glucocorticoid treatment that (1) reflect current and best knowledge available and (2) take into account current clinical practice. We have chosen a question-answer rationale presentation style to convey the messages, to summarise our meeting in a readable format, and to avoid dogmatism.

WHAT TERM SHOULD BE USED TO DESCRIBE THIS CLASS OF DRUGS (STEROIDS, CORTICOSTEROIDS, CORTICOIDS, GLUCOCORTICOSTEROIDS, GLUCOCORTICOIDS)?

Answer

We suggest the use of the term **glucocorticoids**.

Rationale

The term **steroids** is too broad as it simply describes chemical compounds characterised by a common multiple ring structure that include molecules such as cholesterol, sex hormones, and corticosteroids. The terms **corticosteroids** and **corticoids** are insufficiently exact as the adrenal cortex synthesises two classes of steroids: the **corticosteroids** in the narrower sense, which have 21 carbon atoms, and androgens, which have 19 carbon atoms. The adrenal corticosteroids in the narrower sense differ in their relative glucocorticoid (carbohydrate metabolism regulating) and mineralocorticoid (electrolyte balance regulating) activity and were, therefore, historically described as **glucocorticoids** and mineralocorticoids.[6] Corticosteroids are grouped according to their relative potencies in Na^+ retention, effects on carbohydrate metabolism (hepatic deposition of glycogen and glucogenesis), and anti-inflammatory effects.[6] Potencies based on effects on glucose metabolism (but not effects on Na^+ retention!) closely parallel those for anti-inflammatory effects. This was the reason for using the term glucocorticoids where

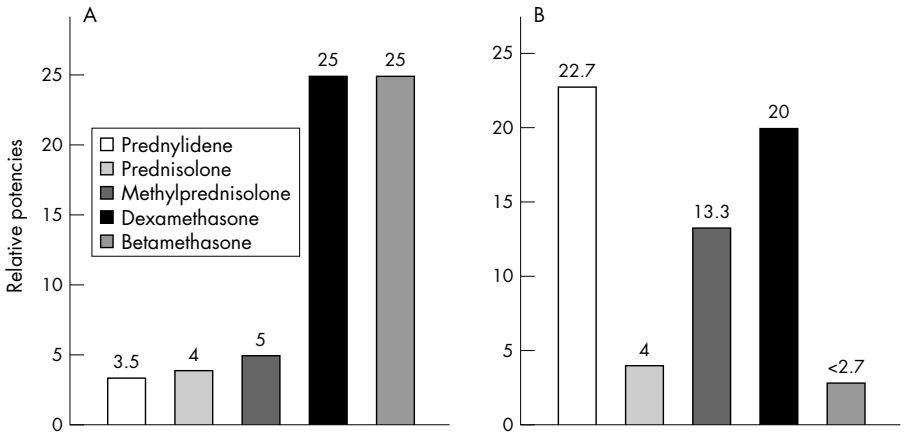

Figure 1 Relative potencies of various glucocorticoids to produce genomic and non-specific non-genomic effects. The figure shows a comparison between genomic and non-genomic potencies of various glucocorticoids. (A) Data for classic (genomic) effects were taken from Goodman and Gilman[6] and are relative to cortisol. (B) Data for non-specific non-genomic effects were taken from Schmid *et al*[8] and are relative to prednisolone. The value for prednisolone was set to 4 and values for the other glucocorticoids were scaled accordingly to allow direct comparison with the classic potencies. It should be noted that non-specific non-genomic effects are especially relevant in higher doses.

anti-inflammation is the therapeutically desired effect. In humans, hydrocortisone (cortisol) is the main glucocorticoid, and aldosterone is the main mineralocorticoid.[6] Glucocorticoids in therapeutic use for anti-inflammatory and immunosuppressive effects are nowadays exclusively synthetic molecules that have pronounced anti-inflammatory potencies compared to relative weak or even zero Na^+ retaining potencies.

For these reasons the terms **glucocorticoid(s)** or **glucocorticosteroid(s)** are scientifically correct and appropriate to describe the use of these drugs for the treatment of rheumatic diseases and other conditions where anti-inflammatory and immunomodulatory effects are desired. However, the term "glucocorticosteroids" is not very often used (only 368 citations in Medline 1994–2000) compared to the term "glucocorticoids" (11 178 citations). In summary, we suggest generally the use of the term **glucocorticoid(s)**.

HOW CAN GLUCOCORTICOID THERAPY SCHEDULES BE DESCRIBED AS PRECISELY AS POSSIBLE?

Answer

We suggest a description that is precise regarding (*a*) the drug, (*b*) the dosage, (*c*) the route of administration, and (*d*) the timing of administration (timing, frequency, duration, sometimes cumulative dosage where appropriate).

Rationale

(*a*) Drug

It is absolutely necessary to provide the full name of the drug, as different glucocorticoid drugs have different drug potencies. Moreover, glucocorticoids produce distinct therapeutically relevant effects. Genomic effects are mediated by cytosolic receptors that alter expression of specific genes. Specific non-genomic effects occur within a few minutes and are mediated by steroid selective membrane receptors. Non-specific non-genomic effects occur within seconds, but only at high glucocorticoid dosages, and seem to result from direct interactions with biological membranes. It should be noted that clinical importance and therapeutic relevance of these rapid glucocorticoid effects remain unclear at present, although current basic research results on their existence are very convincing. More detailed information on these matters are available in a recent review.[7]

Drug potencies are usually described by the equivalent dosages as given in figure 1. The left part of the figure shows the well known relative potencies of important glucocorticoids to produce classic genomic effects. These values have been in use for decades although experimental and clinical evidence for their preciseness is weak. Nevertheless, these relations are usable for daily clinical work in terms of **general therapeutic guidelines**, but their dogmatic use should be avoided. We suggest therefore that (1) these values continue to be used until more exact data are available and (2) doses of different glucocorticoids are expressed by converting them into doses of "prednisone equivalent"; in other words to express doses of different glucocorticoids in mg prednisone (=mg prednisolone, as prednisone is equally as potent as prednisolone) by using the relative potencies given above. The suggestion for further using the term prednisone equivalent is recommended for historical reasons because prednisone was the first synthetic, pharmacologically relevant glucocorticoid drug to be introduced into clinical medicine.

However, (1) It should be noted that the use of equivalent dosages is according to recent data only a valid procedure if doses of less than 100 mg prednisone are considered. At higher doses non-genomic effects come into play. This is important because the relative potencies of different glucocorticoids producing these non-genomic effects are completely different from their classic genomic effects.[2 8 9] Figure 1B shows the data that rationalise the empirical use of glucocorticoids for high dose therapy. For instance, for pulse therapy methylprednisolone is often preferred to prednisolone in exacerbated immunologically mediated disorders. The two drugs have similar genomic potency but in high dose therapy the non-specific non-genomic effect of methylprednisolone is more than threefold stronger. This may explain the empirical clinical preference for methylprednisolone. Another example is the very low non-genomic potency of betamethasone, which may be one reason why this drug is rarely used systemically although it has the same genomic potency as dexamethasone. In summary, the clinical use of different glucocorticoids is clearly determined by their magnitude of clinical efficacy, but one underlying reason for this may be their non-genomic potencies.

(2) For an **individual patient** the dose of the specific drug should be given instead of calculating the prednisone equivalent.

(*b*) Dosage

The dose defines the strength of effects and side effects. This relates to glucocorticoid receptor saturation (the more receptors are occupied the more effect is exerted) and very likely to the occurrence of additional non-genomic effects at higher doses (fig 2).

(*c*) Route of administration

An absolutely necessary specification to be given for describing glucocorticoid therapy is whether the drug is administered orally, intravenously, intramuscularly, or intra-articularly. In this regard we consider intra-articular application as a special form of (local) high dose therapy where local

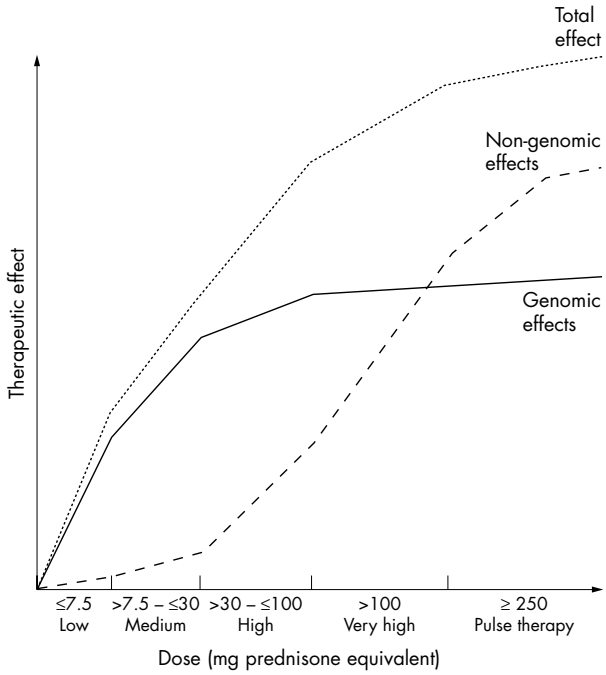

Figure 2 Current view on the dose dependency of genomic and non-genomic effects providing arguments for the description of glucocorticoid dosages. Figure 2 summarises the current knowledge on the occurrence of genomic and non-genomic effects in terms of a dose-response relationship.[1 2 6–10] This provided the basis for our recommendations on how to describe glucocorticoid doses; however, arguments concerning clinical feasibility have been taken into account. Against this background we stress that neither for genomic nor for non-genomic effects is there an exact knowledge of the relationship between dosage, concentration, and cellular and clinical effects (see text). However, this figure represents the result of our interpretation of currently available information on basic research results and clinical practice.

concentrations are reached that can, in addition to the most important genomic effects, also exert non-genomic effects. It should be noted that the range of glucocorticoids available for intra-articular administration is larger than the range for systemic use. Moreover, these intra-articular glucocorticoids differ significantly in structure with important consequences on their therapeutic effects.

(*d*) Time

We consider the following criteria to be of relevance for glucocorticoid effects and side effects:

Timing

At what hour of the day is the glucocorticoid drug given? This question is of special importance against the background of (1) circadian rhythm of endogenous cortisol production, which may be changed in some rheumatic conditions, and (2) also in view of the diurnal variation of symptoms, particularly morning stiffness in inflammatory polyarthritis. Although research in this area of chronobiology is still limited, several findings suggest that our current paradigms about timing of glucocorticoid administration need to be questioned by appropriate investigation, both in terms of efficacy and safety.

Frequency

How often is the glucocorticoid drug given each day—once a day or is there a dose splitting?

Duration

What is the duration of a defined treatment schedule given in days, weeks, months, or even years?

Note that (1) each period of glucocorticoid treatment ("treatment schedule") should be described in these terms, and (2) "tapering" the dose is a frequent procedure either to approach the maintenance dose or to stop the glucocorticoid therapy.

Cumulative dose

Many adverse effects of glucocorticoid treatment (such as glucose intolerance and osteoporosis) are related to cumulative tissue exposure. We therefore suggest describing the cumulative dose, especially in long term therapy. Currently the calculation of cumulative doses is used rather for scientific reasons.

In summary, we suggest that an appropriate description of a given glucocorticoid therapy regimen should follow this example:

Initially x mg prednisone orally once a day (at 8 00 am) for two weeks, then reduced to y mg prednisone a day, followed by . . .(describe each step of reduction in terms of mg and time) reaching zero after for example, one year (overall duration). The cumulative dose was z mg prednisone.

WHAT SHOULD BE THE DEFINITION OF CONVENTIONAL TERMS FOR GLUCOCORTICOID DOSES?

Answer

We suggest the following terminology:

- Low dose ≤7.5 mg prednisone equivalent a day
- Medium dose >7.5 mg, but ≤30 mg prednisone equivalent a day
- High dose >30 mg, but ≤100 mg prednisone equivalent a day
- Very high dose >100 mg prednisone equivalent a day
- Pulse therapy ≥250 mg prednisone equivalent a day for one or a few days.

Rationale

As mentioned above glucocorticoids act via genomic and non-genomic effects.[1 2 7] For genomic effects the degree of cytosolic receptor saturation is considered as a direct modulator of the intensity of (therapeutic) glucocorticoid effects. Unfortunately, there are no precise data available that describe the relationship between administered glucocorticoid dose and consequent occupation of the receptors. Moreover, it has to be taken into account that there is a wide interindividual variation in plasma concentrations where the same single (oral) dose of glucocorticoid is given. However, it has been calculated from known binding constants, free steroid concentrations, and other variables that oral doses of 7.5 mg and 15 mg of prednisolone would result in blood concentrations eight hours after the dose that would bind the receptors to 42% and 63% of saturation, respectively,.[10] According to this calculation, higher doses (for example, 100 mg or more) would be required to result in nearly complete receptor saturation.[10] These considerations led to our proposal above, together with the fact that clinicians in their daily practice have already created landmark glucocorticoid doses that are still cloudy in their definition but clearly group around 7.5, 30, and 100 mg prednisolone equivalent a day. We have used these landmark doses for defining the terminology suggested above for the following reasons (see also fig 2):

Low dose

We consider a low dose glucocorticoid treatment as a treatment with ≤7.5 mg prednisone equivalent a day, because:

- This dose occupies less than 50% of the receptors
- This dose range is often used for maintenance therapy for many rheumatic diseases requiring glucocorticoids[11 12]
- Relatively few adverse effects (such as osteoporosis) are expected.

The recognition that a relative hypocortisolism is present in chronic inflammatory conditions (for example, rheumatoid arthritis, polymyalgia rheumatica)[13] leads some observers to regard low dose glucocorticoid treatment as a means of replacement therapy for the reduced adrenal production.[14]

Medium dose

We consider an administered dose of >7.5 mg, but ⩽30 mg prednisone equivalent a day to be a medium dose, because

- These doses lead to a significantly higher receptor engagement ranging above 50% but below 100%
- Doses between 7.5 mg and 30 mg are effective if given initially in various conditions of rheumatic diseases (primary chronic rheumatic diseases)
- It is a "natural barrier" in the sense that most rheumatologists do not initially treat most patients (for example, those with non-complicated rheumatoid arthritis or polymyalgia rheumatica) with doses above 30 mg[15]
- Side effects are considerable and dose dependent in this range if treatment is given for longer periods

High dose

We consider doses between >30 mg and ⩽100 mg prednisone equivalent a day to be high doses, because:

- These doses significantly increase receptor saturation in a dose dependent manner resulting in an almost complete receptor saturation at approximately 100 mg/day where up to 100% of genomic glucocorticoid effects are assumed to be exerted[10]
- High doses as defined above are usually and successfully given as initial treatments for subacute rheumatic diseases such as non-life threatening exacerbations or visceral complications of rheumatoid arthritis or other connective tissue diseases[16 17]
- These doses cannot be administered for long term therapy because of the occurrence of severe side effects

Very high dose

We consider doses >100 mg prednisone equivalent a day to be very high doses, because:

- Above 100 mg prednisone equivalent a day there is virtually a 100% receptor saturation with regard to cytosolic receptors. Therefore, a further increase in dose may affect the pharmacodynamics (for example, receptor off loading and re-occupancy), receptor synthesis, and expression, but may also bring additional therapeutic benefit via other mechanisms. This assumed additional therapeutic benefit of very high doses could be obtained via qualitatively different, non-genomic effects. These effects are either mediated by membrane bound receptors or are initiated by physicochemical interactions with cellular membranes.[1 2 7] It is not yet clear if these effects are directly of therapeutic relevance, but experimental data suggest that these differential effects come increasingly into play above around 100 mg/day (figs 1 and 2)
- These doses are often successfully given as initial doses for acute or life threatening exacerbations of rheumatic diseases such as connective tissue diseases, vasculitis, and rheumatoid arthritis.[17–19]
- These doses cannot be given for long term treatment because of the occurrence of dramatic side effects.

Pulse therapy

We consider "pulse therapy" as a specific therapeutic entity that refers to the administration of ⩾250 mg prednisone equivalent a day (usually intravenously) for one or a few (usually ⩽5) days. It should be stressed that this term rather refers to the very high dose given than to its intermittent character in terms of time. We have the following arguments to support this suggestion. The first is that in common clinical practice doses of 250 mg/day or above are usually only used in terms of pulse therapy. Thus these doses are exclusively given for a few days, but then reduced or stopped directly. The second argument is that at these doses non-genomic potencies of glucocorticoids come into play. It is likely that these are the reasons for the clinical finding that generally very high dosages and pulse therapy are successful in acute exacerbations of immunologically mediated diseases. The immediate effects produced by very high dosages could be additive to the genomic effects mediated by cytosolic glucocorticoid receptors. The additional quantum of inhibition of the excessive immune processes could make a crucial contribution to the therapeutic effect by helping to terminate the acute exacerbation. In rheumatology and clinical immunology, acute episodes or particularly severe forms of rheumatic diseases such as systemic lupus erythematosus, vasculitis, polymyositis, and rheumatoid arthritis are examples of the circumstances where very high doses or pulse glucocorticoid therapy can be successful.[17–19] Pulse therapy results in termination of the exacerbation or regression of severe forms of disease in a high proportion of cases with a relatively low incidence of side effects. Non-genomic mechanisms of glucocorticoid action may also provide an explanation for the beneficial therapeutic effect of pulse glucocorticoid therapy for many other indications. These include the treatment of acute spinal injuries and use in immune thrombocytopenia, juvenile dermatomyositis, juvenile chronic arthritis, optic neuritis, rapid progressive glomerulonephritis, and pemphigus vulgaris. Non-genomic mechanisms offer a possible explanation for benefits, such as very early clinical response, which cannot be extrapolated from the dose-response effects of medium or low dose therapy.

CONCLUSION

These proposals for nomenclature of glucocorticoid treatment are made in the hope that scientific consensus and clarity can be improved and that the nomenclature relates in some way to mechanisms of action. We stress that our proposals are tentative, but are consistent with current knowledge. Although glucocorticoids have immense therapeutic benefits and are widely used, many issues remain to be clarified. These include their detailed mechanisms of action, and the rationale for the use of various doses/regimens or measures to reduce adverse effects. Accordingly, much effort will need to be invested to obtain greater insight, and this will then guide any future revision of the nomenclature.

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ECHO

Keeping up appearances

Please visit the Annals of Rheumatic Diseases website [www.annrheumdis.com] for link to this full article.

Biopsy of the temporal artery can be used to confirm giant cell arteritis (GCA) well after corticosteroid treatment has started, according to a small prospective study. The findings will need to be verified by a larger study, but it now seems that treatment need not be delayed for a biopsy for fear of compromising the histological picture. Usually, a biopsy is performed within two weeks of starting treatment.

Temporal artery biopsy specimens from nine of the 11 patients in the study showed features of GCA—that is, giant cells in the intima and media, lymphocytes and histiocytes in the media, reduplication or fragmentation of the internal elastic lamina, and thickening of the intima. In two of the nine the appearance indicated healed GCA. Three of four specimens (75%) were positive within two weeks after starting corticosteroid treatment and six of seven (86%) after 4–6 weeks.

The patients received a standardised regimen of high dose corticosteroids according to whether they had visual loss on referral or not. At entry to the study they were randomised to receive biopsy before treatment; within in week after treatment started; at 2–3 weeks; and at 4–6 weeks. Patients were receiving at least 40 mg prednisolone when undergoing biopsy. Each paraffin block of biopsy material was cut at 4–5 μm thickness in at least three levels for staining and histological examination.

Previously there has been controversy about whether corticosteroid treatment obscures the pathological features of biopsy material, but this has been based on retrospective studies.

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