Glucocorticoids in rheumatology: indications and routes of administration

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ABSTRACT

This paper in short reviews general indications, doses and routes of administration of glucocorticoid therapy in rheumatology. It presents greater detail concerning intralesional and intra-articular glucocorticoid injections.

Introduction

Since the discovery of cortisol in 1948, glucocorticoids in various dosages and routes have been widely used for rheumatic diseases, varying from the acute gout attack and generalised immune arthritides to collagen diseases and systemic vasculitides. This paper provides a short overview of indications and routes of administration. We will present greater detail concerning intralesional and intra-articular glucocorticoid injections, because this topic is not covered elsewhere in this issue.

Indications

The aims of glucocorticoid therapy differ for the various rheumatic diseases for which they are applied; they range from symptomatic relief and disease-modifying effects to immunosuppressive and immunomodulatory actions. These aims are related to routes of administration, pharmacological properties, pharmacokinetics, and doses of glucocorticoids. Based on pathophysiological and pharmacokinetic data, standardisation of nomenclature has been proposed to minimise problems in interpretation of generally used terms like “low” or “high” dose, see Table I (1). The dose and routes of administration are not only related to the aims of therapy and clinical efficacy, but also to the risk of adverse effects and the speed of onset of action. High doses of glucocorticoids next to genomic actions, which take some time to develop, also have non-genomic actions, occurring within minutes after administration.

Table II gives an overview of general use of glucocorticoids in rheumatology. Without more detailed description, some of the indications could at first glance be considered as questionable. For instance, in systemic sclerosis glucocorticoids, especially in high dosages are contraindicated because of the risk of scleroderma renal crisis (2), but they may be useful for myositis or interstitial lung disease complicating systemic sclerosis. The table shows that glucocorticoids are basic part of the therapeutic strategy in myositis, polymyalgia rheumatica and systemic vasculitis. Moreover, they are used in increasing frequency in therapeutic strategies for rheumatoid arthritis. For other diseases, glucocorticoids are only adjunctive therapy or are not used at all. In osteoarthritis, for example, glucocorticoids are not given, except for intra-articular injection when there are signs of synovitis of the osteoarthritic joint (3). For generalised non-inflammatory soft-tissue disorders, glucocorticoids are not indicated, and for localised soft-tissue disorders for intralesional injection only.

Doses and routes of administration

In rheumatology, several routes of administration are used for specific diseases and indications/complications, ranging from systemic oral, intramuscular and intravenous glucocorticoid therapy to local injections. These are discussed in short here; the usage of systemic glucocorticoid therapy for specific rheumatologic diseases will be discussed into detail in the other articles of this issue.

Oral low to high glucocorticoid therapy

Regarding the application of glucocorticoids in generalised immune arthritides, like rheumatoid arthritis, psoriatic arthritis and juvenile idiopathic arthritis, most data have been published on the use in rheumatoid arthritis. Glucocorticoids are given for their symptomatic effect and joint sparing

Table I. Terminology of glucocorticoid dosages.[1]

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

Table II. General use of glucocorticoids in rheumatology.

	*initial** oral dose			intravenous, very high dose* or pulse	intra-articular injection
	low*	medium*	high*		
Arthritides					
gouty arthritis, acute	–	2	2	–	2
juvenile idiopathic arthritis	–	1	1	–	1
osteoarthritis	–	–	–	–	1
pseudogout	–	–	–	–	2
psoriatic arthritis	–	1	–	–	2
reactive arthritis	–	–	–	–	1
rheumatic fever	–	1	1	–	–
rheumatoid arthritis	2	2	1	1	2
Collagen disorders					
dermatomyositis, polymyositis	–	–	3	1	–
mixed connective tissue disease	–	1	–	1	1
polymyalgia rheumatica	–	3	–	1	–
Sjögren's syndrome, primary	–	–	1	–	–
systemic lupus erythematosus	–	2	1	1	–
systemic sclerosis	–	1	–	–	–
Systemic vasculitides					
in general	–	–	3	1	–

*initial dose: dose at the start of therapy, will often be decreased in time depending on disease activity; dose in prednisone equivalents a day: low: ≤7.5 mg, medium: >7.5 but ≤30 mg, high: >30 but ≤100 mg, very high: >100 mg.
–: rare use; 1: infrequent use, for therapy resistant disease, complications, severe flare, major exacerbation, and for bridging the lag-time of recently started therapy; 2: frequently added to / used as the basic therapeutic strategy; 3: basic part of the therapeutic strategy.

properties: disease-modifying effects. These latter effects have been proven only for therapy during the first 2 years of rheumatoid arthritis, which is not to say these effects must be absent when treating patients with glucocorticoids in a later phase of their disease: it has not yet formally been investigated. The radiological gain of the first two years with glucocorticoids is kept during the following years.

Glucocorticoids are always combined with other disease-modifying drugs in early rheumatoid arthritis. In general, two dosing regimes can be discriminated in this phase of the disease: low or medium dosing, up to 10 mg of prednisone-equivalent per day unchanged during the two years and high starting doses, e.g. 60 mg/day, with tapering off and stopping. This latter scheme reflects a step-down strategy. Advantages of a step-down strategy when compared with step-up strategies are that the former strategy optimally takes advantage of the 'window of opportunity' and that symptom relief occurs very quickly and effectively. Drawbacks are that tailoring medication to the individual patient's disease activity is not possible: every patient starts with the same intensive therapy. Another drawback is the higher risk of adverse effects of high-dose glucocorticoids, like psychosis (4).

Not only in early RA, but also for more longstanding RA intensive disease control with disease-modifying anti-rheumatic drugs (DMARDs) including glucocorticoids in daily practice has been shown to be beneficial (5).

Next to usage in generalised immune arthritides, oral glucocorticoid therapy is also used to treat the acute gout attack, especially in patients with contraindications for non-steroidal anti-inflammatory drugs and colchicine. For this use, typically 30–35 mg of prednisone equivalent during 5 days is applied, especially by general practitioners. A problem of this therapy arises when given for the presumed diagnosis gout attack, when in fact the true diagnosis is septic arthritis; furthermore, coincident septic and gouty arthritis have been described. So this therapy seems only safe if the risk of (coincident) septic arthritis is very low, *e.g.* by detecting urate crystals by polarisation microscopy in the joint fluid and having negative tests for bacterial infection. In the first instance, naked eye inspection will do: if no clear pus, glucocorticoids could be given. If the culture after some days nevertheless is positive, not too much time is lost before starting antibiotic therapy. Therefore, diagnostic joint aspiration with naked eye inspection, crystal assessment, and culture is indicated for optimal safety of glucocorticoid therapy of gout attacks. When the needle is positioned intra-articularly for this purpose, it is easier and probably more safe and effective to inject a glucocorticoid after aspiration, compared to giving a high dose of oral glucocorticoids afterward. So in our view, indications for oral glucocorticoid therapy of the gout attack are limited.

Oral, intravenous and intramuscular glucocorticoid pulse therapy

Pulse therapy with glucocorticoids is used in rheumatology, especially for remission induction or treatment of flares of collagen disorders and vasculitides, see Table II. In RA, pulse therapy is applied to treat some of the serious complications of the disease and to induce remission in active disease, often in the initiation phase of second-line antirheumatic treatment. In the latter patients, pulse therapy with schemes of 1000 mg methylprednisolone intravenously or equivalents has been proven to be effective in most studies. Although the duration of the effect shows large variation among individuals, the beneficial effect generally lasts for about 6 weeks (6).

It thus only seems sensible to apply pulse therapy in active RA, if there is also made a change in the therapeutic

Table III. General directions on materials and doses for intra-articular, peri- and intralesional injections (10).

Disorder / site	Syringe (cc)	Needle (G, length)	Triamcinolone (40 mg/ml)	Lidocaine
Arthritis small joint	1	25 G, 1.6 cm (5/8")	0.2–0.5 cc	none
Arthritis large joint	2	21 G, 5-7 cm (2")*	1 cc	1 cc, 2%
Enthesis, general Tenosynovitis	1	25 G, 1.6 cm (5/8")	0.25 cc	0.75 cc, 2%
Fasciitis plantaris	5	21 G, 5 cm (2")	0.5 cc	2 cc, 2%
Subacromial space	5	21 G, 5 cm (2")	1 cc	4 cc, 2%
Biceps tendon Bursitis, general	2	23 G, 3 cm (1¼")	1 cc	1 cc, 2%
Epicondylitis	2	25 G, 1.6 cm (5/8")	0.5 cc	1.5 cc, 2%
Finger flexor tendon	1	25 G, 1.6 cm (5/8")	0.5 cc	0.5 cc, 2%
Greater trochanter	10	21 G, 5 cm (2")**	1 cc	9 cc, 1%
Carpal tunnel	1	25 G, 1.6 cm (5/8")	0.5 cc	none
Meralgia paresthetica	5	23 G, 3 cm (1¼")	1cc	4 cc, 2%

*19 G for arthrocentesis (aspiration); **longer in obese patients.

strategy, *e.g.* with second-line antirheumatic treatment, aimed to stabilise on the long term the remission induced by the pulse therapy. The short-time effects of pulse therapy in patients with established, active RA on various dimensions of health status closely resemble the long-term effects of effective conventional DMARD therapy such as methotrexate in patients with early RA (7).

Treatment with subcutaneous synacthen (a synthetic form of adrenocorticotropic hormone) stimulating the secretion of endogenous glucocorticoids theoretically carries a lower risk of adrenal atrophy compared to glucocorticoid (bridging) therapies, but this therapy is not applied frequently nowadays (8, 9).

The risk of some of the adverse effects of pulse therapy is not the same for all rheumatic disorders. In SLE, osteonecrosis and psychosis seem to be more frequent side-effects of pulse therapy compared to patients with RA (7). However, osteonecrosis and psychosis can also be complications of SLE itself. Another paper of this issue goes into detail of adverse events of glucocorticoid pulse therapy.

Intralesional and intra-articular glucocorticoid injections (10)

Injections with glucocorticoids are widely used for arthritis, tenosynovitis, bursitis, enthesitis and compression neuropathies like carpal tunnel syndrome (Table III). Most indications, recommendations and data on efficacy regarding local injections are not based on clinical trials, but on theoretical arguments and clinical experience. It is recommended that intra-articular glucocorticoid injections be repeated no more often than once every 3 weeks and be given no more frequently than 3 times a year in a weight-bearing joint (*e.g.* the knee) to minimise glucocorticoid-induced joint damage. Nonetheless, in clinical practice not seldom intra-articular glucocorticoid injections more frequently have been and are applied into weight-bearing joints without clinical problems. Administration of a local anaesthetic like lidocaine concurrently with intra-articular or soft tissue injection of a glucocorticoid may provide immediate relief of pain. Glucocorticoids soluble in water (*e.g.* phosphate salts) have a more rapid onset of action with probably less risk of subcutaneous tissue atrophy and depigmentation of the skin when given intralesionally. Insoluble glucocorticoids are longer acting and might decrease soft tissue fibrous matrix more and should thus be used with caution in superficial localisations with thin overlying skin, especially in elderly, and patients with peripheral vascular disease. A strategy then is to dilute the concentration of the glucocorticoid by adding lidocaine and to inject a small volume. Insoluble glucocorticoids are given more safely into deep sites.

In general, the effect of glucocorticoid injection probably depends on several factors, like the underlying disease (*e.g.* RA or osteoarthritis) or indication, the treated joint (size, weight bearing or non-weight bearing), the activity of arthritis, the volume of synovial fluid in the treated joint, application of arthrocentesis (synovial fluid aspiration) before injection, the choice and dose of the glucocorticoid preparation, and last, but not least application of rest to the injected joint and the injection technique. The effect of injections seems to be less favourable in osteoarthritis compared with RA (11). Arthrocentesis - the puncture of a joint cavity with aspiration of fluid - before injecting the glucocorticoid preparation reduces the risk for relapse of arthritis (12). Triamcinolone hexacetonide, among the injectable glucocorticoids the least soluble preparation, shows the longest effect (11, 13, 14). Based on the literature, no definite evidence-based recommendation can be made, but it seems prudent to rest and certainly not to overuse the injected joint or site, even if pain is relieved.

The reported infection rate of joints following local injections with glucocorticoids is low, ranging from 1 case in 13,900–77,300 injections (15-17). In a prospective study during 3 years in an urban area of 1,000,000 people in the Netherlands, bacterial infection was diagnosed in 214 joints of 186 patients, but only three of these infections could be attributed to an intra-articular injection (18). Other adverse effects of local glucocorticoid injections are *systemic* adverse effects of the glucocorticoid, such as disturbance of the menstrual pattern (19), hot flushes-like symptoms at the day of or the day after injection (20), and hyperglycemia in diabetes mellitus (21). *Local* complications include subcutaneous fat tissue atrophy (especially after improper local injection) (22), local depigmentation of the skin (23), tendon slip and tendon rupture (11, 24), and lesions to local nerves (25).

Conclusion

Glucocorticoids still are the mainstay of therapy in many various rheumatic diseases. Knowledge on indications, dosages and routes of administration is essential for optimal application of this therapy.

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