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Intra-articular Glucocorticoid Treatment

Efficacy and Side Effects

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Abstract

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Intra-articular glucocorticoid injection therapy is frequently used to relieve symptoms of arthritis, but there is considerable variation in injection routines among physicians. One issue of debate concerns the importance of synovial fluid aspiration during the injection procedure. In the present randomised controlled study of patients with rheumatoid arthritis (RA), a significantly reduced risk for arthritis relapse was observed when arthrocentesis was included in the intra-articular injection procedure of the knee.

Furthermore, there is no consensus about the post-injection regimes. Previous studies have shown beneficial effects of post-injection rest of the knee, but also injection routines for other joints often include such recommendations. The present randomised controlled trial showed that 48-hour rest in elastic orthosis after intra-articular injection in the wrist did not improve the outcome. Thus, the effect of post-injection rest varies between different joints.

The improved treatment result of post-injection rest of the knee is supposed to be caused by retarded steroid resorption from the joint. In order examine the metabolic effects in cartilage, bone and the hypothalamic-piuitary-adrenal (HPA)-axis, resting and mobile RA patients were studied after intra-articular knee injections. Serum levels of the injected glucocorticoid, triamcinolone hexacetonide (THA), were analysed, as well as cartilage oligomeric matrix protein (COMP) as a marker of cartilage turnover, osteocalcin for bone formation and deoxypyridinoline for bone resorption. The HPA-axis was assessed using serum levels of cortisol and adrenocorticotropine hormone. The result showed a short term and reversible suppression of the HPA-axis and bone formation, whereas bone resorption was unaffected. No differences between mobile and resting patients were observed. In both groups reduction of COMP levels were seen, but these were significantly more pronounced in resting patients, suggesting a cartilage-protective effect. The THA levels increased similarly in both groups, indicating that rest did not affect glucocorticoid resorption.

Consequently, another explanation for the beneficial effects of postinjection rest of knee synovitis should be considered. In the present material the incidence of infectious complications of intra-articular treatment was less than 1/12,000 injections.

The findings in this thesis can be applied in the clinical practice and should be considered when new guidelines for intra-articular glucocorticoid therapy are created.

Keywords: arthritis, intra-articular glucocorticoid, triamcinolone hexacetonide, arthrocentesis, bone metabolism, cartilage, cortisol, ACTH, joint infection

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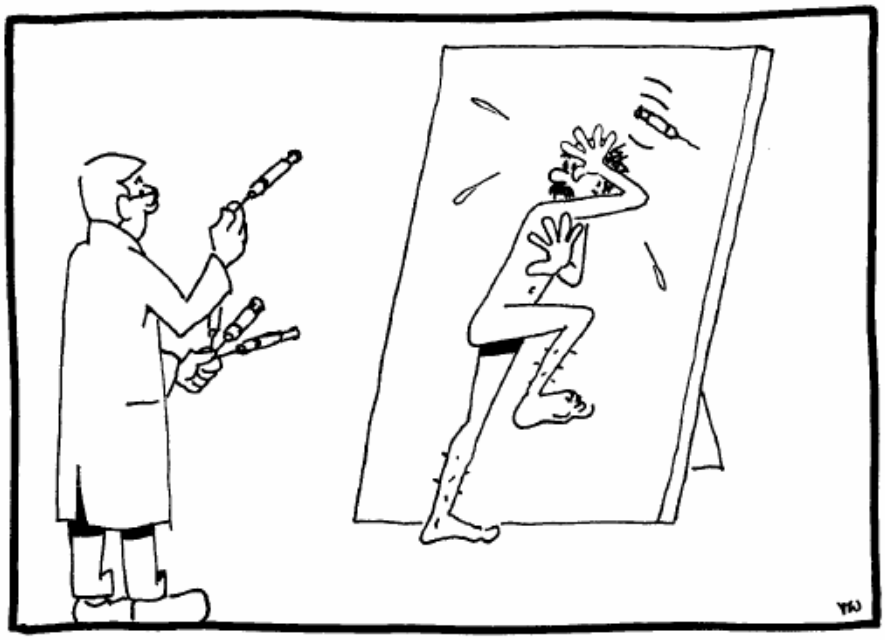
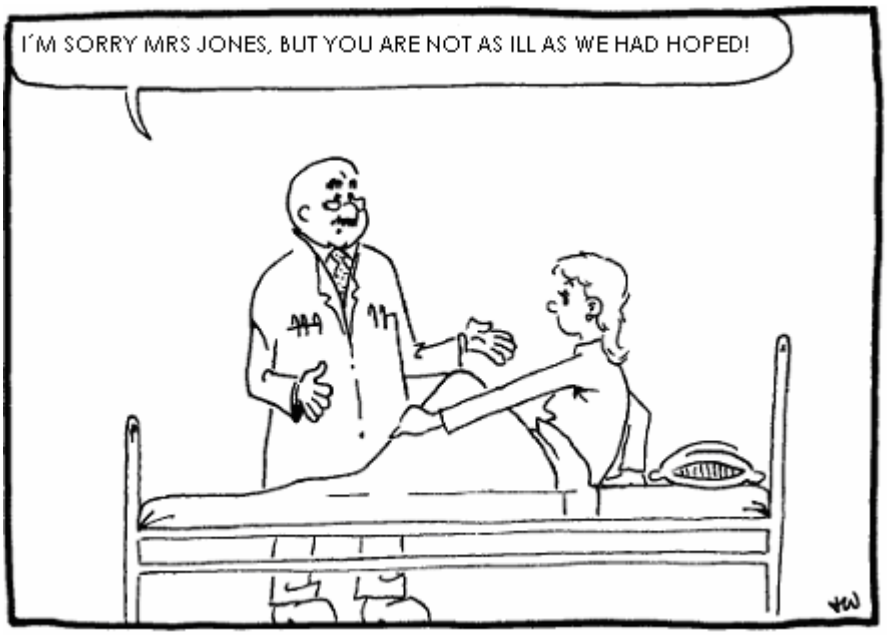
To my beloved family

Katarina and Ulrika

Pottholzt: The injection technique is crucial.(Gefle Dagblad 20/10 2000)



Pottholzt: There are many difficulties in patient recruiting for clinical trials. (Gefle Dagblad 15/5 2002)



LIST OF REPORTS

The present thesis is based on the following reports, which will be referred in the text by their Roman numerals:

I **Weitoft T, Uddenfeldt P.** Importance of synovial fluid aspiration when injecting intra-articular corticosteroids. *Ann Rheum Dis 2000; 59: 233-235.*

II **Weitoft T, Rönnblom L.** Randomised and controlled study of post-injection rest following intra-articular glucocorticoid treatment for wrist synovitis. *Ann Rheum Dis 2003; 62: 1013-1015.*

III **Weitoft T, Larsson A, Saxne T, Rönnblom L.** Changes of cartilage and bone markers after intra-articular glucocorticoid therapy with and without post-injection rest in patients with rheumatoid arthritis. *Ann Rheum Dis Published Online First: 20 April 2005. doi:10.1136/ard.2004.035022*

IV **Weitoft T, Rönnblom L.** Glucocorticoid resorption and effects on the hypothalamic-pituitary-adrenal axis after intra-articular treatment of the knee in mobile and resting patients. *Submitted.*

V **Weitoft T, Mäkitalo S.** Bacterial arthritis in a Swedish health district. *Scand J Inf Dis 1999; 31: 559-561.*

Abbreviations

ACTH	Adrenocorticotropine Hormone
BAP	Bone-specific Alkaline Phosphatase
COMP	Cartilage Oligomeric Matrix Protein
CRH	Corticotropine Releasing Hormone
CRP	C-Reactive Protein
DMARD	Disease Modifying Anti-Rheumatic Drugs
ESR	Erythrocyte Sedimentation Rate
HAQ	Health Assessment Questionnaire
HLA	Human Leukocyte Antigen
HPA	Hypothalamic-Pituitary-Adrenal
ICAM-1	Intercellular Cell Adhesion Molecule-1
IL	Interleukin
MCP	Metacarpophalangeal
MP	Methylprednisolone
MRI	Magnetic Resonance Imaging
MTP	Metatarsophalangeal
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
PIP	Proximal Interphalangeal
PRWE	Patient Rated Wrist Evaluation
RA	Rheumatoid Arthritis
RNA	Ribonucleic acid
SHBG	Steroid Hormone Binding Globulin
TA	Triamcinolone Acetonide
THA	Triamcinolone Hexacetonide
TNF	Tumor Necrosis Factor
UK	United Kingdom
US	United States

Contents

INTRODUCTION

Intra-articular corticosteroid treatment is frequently used to relieve inflammatory joint symptoms such as pain, heat, swelling and effusion. On the right indication, impressive therapeutic results can be obtained in the short term, and it has therefore become an important tool in the treatment of arthritis.

The injection technique is easy to learn, to perform and has widespread usage. Many physicians, including rheumatologists and general practitioners, benefit from knowing how to use the method properly. Compared to treatment with non-steroidal anti-inflammatory drugs (NSAID), the symptom-relieving effect appears rapidly, the costs are low and serious side effects are few. The release of glucocorticoid into the circulation also provides some general improvement to the patient. The appeal of the injection therapy has increased with the growing emphasis on early disease control in rheumatoid disease.

Despite the widespread usage, it is surprising that there has been so little attention given to the injection procedure. The scientific documentation in this field is sparse. The recommendations in the literature are based more on tradition and clinical experience than on evidence-based medicine. The injection therapy could probably be used more adequately with more knowledge of the optimal injection routines.

There is also a lack of knowledge of how intra-articular corticosteroid injections influence different metabolic systems.

This thesis deals with different aspects of the steroid injection procedure, as well as the infectious and metabolic side effects. The findings will increase the knowledge of how to enhance the therapeutic outcome with maximal control over possible adverse reactions.

BACKGROUND

Arthritis

The normal joint

The function of a joint is to allow movement between two adjacent bones. A normal synovial joint consists of two opposing bones with surfaces of articular cartilage.

The role of cartilage is to minimize friction during movement and to absorb shock associated with loading. The tissue consists of a fluid phase composed of water and electrolytes (up to 85% of wet weight), and a solid phase composed of collagen (mainly type II collagen), proteoglycans, glycoproteins, other matrix proteins and chondrocytes (1, 2).

The joint is surrounded by a capsule, which on the inside is covered by a thin synovial membrane. This membrane consists of two cell-types, the macrophage-like cells and the fibroblast-like cells. It has a function as an ultrafilter for plasma and produces the synovial fluid. The fluid conveys nutrients for the chondrocytes in the avascular cartilage and removes cartilage degradation products. It also contains hyaluronan and lubricin, molecules important for joint lubrication. The clearance of synovial fluid is made by the lymphatic system (1, 3).

The inflamed joint

In arthritis disease both the innate and adaptive immune system play a prominent role in the disease process (4-6). The inflamed synovium is infiltrated by activated macrophages, producing proinflammatory molecules such as tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1). The macrophages are also potent phagocytes and can act as antigen-presenting cells. Cells of the adaptive immune system, T- and B-cells, are recruited from peripheral blood. The cells bind to adhesion molecules on vascular endothelial cells and migrate through the walls of the capillaries to reach the site of inflammation. They are accumulated in the synovium and T cells become the most dominating celltype of synovitis, consisting of 30-50% of all synovial cells. The cellular infiltration may be associated with formation of germinal center-like structures in the synovium (6).

A large synovial volume increases the intra-articular pressure, which may cause reduced synovial blood perfusion resulting in synovial hypoxia and accumulation of toxic metabolites. This may contribute to the maintenance of the chronic inflammatory process (1, 7).

As a consequence, there is an invasion of newly formed blood vessels, which supports the synovial hyperplasia and facilitates the recruitment of immune cells from peripheral blood. The blood flow is increased and an excess of synovial fluid may be produced (4, 5).

The inflamed synovium also contains proliferating fibroblast-like synoviocytes that produce proteolytic enzymes, such as metalloproteinases. These proteases are involved in the destruction of cartilage and bone. The mass of low differentiated fibroblasts, the pannus, has a tumor-like growth infiltrating cartilage and bone and contributes to the rheumatic joint destruction (8). TNFα, IL-1 and possibly also other cytokines stimulate bone-resorbing cells, osteoclasts, which create the characteristic bone erosions found at radiological examinations of rheumatoid joints (9).

Inflammation and destruction are considered as two different, but mostly parallel, processes. However, joint destruction may occur without signs of inflammation and vice versa (10, 11), illustrating the complex disease process in arthritis.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is the most common chronic polyarthritis in humans (12). The diagnosis is based upon international criteria defined by the American College of Rheumatology (ACR) in 1987 (13). See Table I. RA is predominantly affecting women with a prevalence in Sweden of 0.5-1.0 % and an annual incidence of 25/100 000 inhabitants (14). Epidemiological studies presented during the last decade indicate that the worldwide incidence is decreasing (15, 16).

RA may cause progressive joint destruction, pain, loss of mobility and inability to perform the activities of daily living. It is also a systemic disease and in addition to the articular involvement it may affect many vital organs, which may result in disability, increased morbidity and mortality. Life expectancy for patients with RA is reduced with 5-10 years (12).

The etiology is still unknown. Many theories, including infectious agents and autoantigens as well as genetic, hormonal and environmental factors have been presented over the years. Human cartilage glycoprotein 39, collagen type II and citrullinated peptides are examples of possible autoantigens (6, 17). However, it has not been possible to relate the disease to one single pathogen. It is now suggested that the development of RA depends on a combination of interplaying autoreactive, genetic and environmental factors (6, 17, 18).

Table 1.

The ACR- criteria for diagnosis and classification of RA.. At least 4 of the 7 listed criteria must be fulfilled for the diagnosis. Criteria 1-4 must have been present for at least 6 weeks.

1. Morning stiffness - at least 1 hour before maximal improvement.
2. Arthritis in three or more joints – simultaneously present soft tissue swelling or fluid observed by a physician.
3. Arthritis of hand joints – swelling of wrists, metacarpophalangeal joints (MCP) or proximal interphalangeal joints (PIP).
4. Symmetric arthritis – simultaneous involvement of the same joint areas (defined in 2) on both sides of the body (bilateral involvement of PIP, MCP or metatarsophalangeal (MTP) joints is acceptable without absolute symmetry).
5. Rheumatoid nodules – subcutaneous nodules over bony prominences, extensor surfaces or in juxta-articular regions, observed by a physician.
6. Serum rheumatoid factor – detected by a method positive in less than 5% of normal controls.
7. Radiographic changes – typical of RA on posteroanterior hand and wrist radiographs; it must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints.

Historical aspects on local arthritis treatment

Local joint treatment was used long before the era of treating arthritis disorders with disease modifying anti-rheumatic drugs (DMARD). Beside the recommendations of resting the inflamed joints, various fomentations with herbs and spices were added. In Sweden, rye-flour porridge and white cabbage fomentation were used to relieve rheumatic pain and swelling (19).

Topically applied extracts from rosemarin in combinations with sea salt are still used in antroposophic medicine (20).

Salicylic acid as a symptom relieving substance was introduced in the 19th century. During the last century other NSAID have been developed and mainly been used as orally administered drugs. Serious renal and gastrointestinal side effects have been a problem and have been limiting the use of the drugs. However, in gel, cream or ointment they can also be topically applied and studies have shown beneficial effects on local pain conditions, including arthritis disorders (21).

Intra-articular administration of several drugs, including NSAID´s (22) and DMARD´s, such as gold (23), methotrexate (24) and cyclophosphamide (25), have been studied in arthritis patients. Recently biological preparations, such as antibodies to TNF-α, have been investigated (26). Most of the drugs have been ineffective or harmful and are no longer used.

When the corticosteroids were introduced in the late 40´s, it did not take long before the dramatic effects of relieving arthritic symptoms were discovered (27), both when administered systemically and locally direct into the inflamed joint.

Other substances, such as osmic acid (28, 29) and the radioactive isotope yttrium-90 (29, 30) are also administered intra-articularly, and are still used in the clinical practice in order to achieve a chemical synovectomy. However, they are only used in cases resistant to the intra-articular glucocorticoid therapy.

Importance of glucocorticoids in the human body

The hypothalamic-pituitary-adrenal axis

Endogenous cortisol is produced in the cortex of the adrenal gland and plays an important role for the metabolism of carbohydrates, protein and fat in the human body. Glucocorticoids have multiple effects in different tissues and are essential for survival. By increasing hepatic gluconeogenesis, inhibition of insulin effects and stimulation of lipolysis, they prepare the body and provide energy for flight and fight, including arousal effects of the mind (31, 32).

The secretion of cortisol from the adrenal cortex is dependent upon stimulation by the adrenocorticotropine hormone (ACTH) produced in the pituitary gland. This in turn is stimulated by corticotropine releasing hormone (CRH) produced in the hypothalamus of the brain. The interactions of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nerve

system maintain the basal and stress related homeostasis in the body (32). The normal secretion of the hormones in the HPA-axis follows a circadian rhythm, with a peak in the early morning (33-35).

ACTH has a very short half-life in plasma and the effects on the adrenals are immediate. ACTH binds to specific receptors in the cortical adrenal cells and activates intracellular adenylcyclase leading to a fast stimulation of the steroid synthesis followed by hormone secretion. Most of the glucocorticoids in plasma are inactive and bound to steroid hormone binding globulin (SHBG). By diffusion the free glucocorticoid portion easily passes through cellular membranes and binds to the intracellular glucocorticoid receptors where it can exert its action. The excess of free steroid is eliminated via renal excretion, but most of the glucocorticoids are metabolised in the liver and the inactive metabolites are excreted in urine (31).

Increased plasma level of cortisol gives a negative feedback signal to the hypothalamus and the pituitary gland decreasing the production of CRH and ACTH, respectively. High doses of exogenous glucocorticoids also influence the HPA-axis and suppress the adrenal cortisol production.

Cortisol and the immune system

During the last decades, the knowledge of the interaction between the immune system and the HPA-axis has increased enormously. Glucocorticoids influence the traffic of circulating leukocytes and inhibit many functions of leukocytes and immune accessory cells (32, 36-39). For instance, they suppress the activation of helper T cells and inhibit the production of several cytokines and other mediators of inflammation. They also inhibit the expression of adhesion molecules and their corresponding receptors and potentiate the acute phase reaction (32, 40).

Most of these effects are depending on alterations of the transcription rates of glucocorticoid responsive genes or changes in the stability of messenger-RNA of inflammatory proteins (41). A complex interaction between the glucocorticoid receptor and the transcription factors nucleus factor κB and activator protein-1 inhibits the gene transcription of multiple cytokines, cytokine receptors, chemotactic proteins and adhesion molecules, such as TNF-α, IL-1β, IL-2, IL-6, intercellular adhesion molecule-1 (ICAM-1). Suppression of the phospholipase A_2, cyclooxygenase 2, and nitric oxide synthase 2 genes (32, 38, 42) by glucocorticoids decreases the production prostaglandins, platelet activating factor and nitric oxide, which are key molecules in the inflammatory response.

In addition, there is a non-genomic glucocorticoid activity inhibiting the cycling of sodium and calcium across the plasma membrane, which influences intracellular processes essential for the activity of lymphocytes (43). This mechanism appears when cells are exposed to high glucocorticoid con-

centrations and may therefore be important for the local effect of intra-articular corticosteroid therapy.

The inflammatory response, which can be viewed as a stress signal, stimulates hormone production in the HPA-axis. Three cytokines (TNF-α, IL-1 and IL-6) account for most part by stimulating CRH production in the hypothalamus, leading to higher levels of ACTH and cortisol in plasma. In addition, IL-6 acts synergistically with glucocorticoids in stimulating the acute phase response (32).

The HPA-axis in rheumatoid arthritis

Patients with RA have lower cortisol production than expected (44). Furthermore, the response of the HPA-axis to stress stimuli, such as major surgery, is weak (45). It is unclear whether the hypofunction of the HPA-axis is mainly at the central or at the adrenal level (46-48). The lymphocytes of RA patients have less glucocorticoid receptors (49), and the circadian rhythm of glucocorticoid production is disturbed in periods with active disease and a raised acute phase reaction (50). These findings might be the result of adaptation to the chronic inflammation, but could also be related to genetic or constitutional factors (47). It has been suggested that the defects in the HPA-axis may contribute in the pathogenesis of RA (44).

Intra-articular glucocorticoid treatment

Kendall and Hench in the US and Reichstein in Switzerland received the Nobel Prize in 1950 for the purification and clinical introduction of cortisone in the therapy of RA. Already in the late 1940s, Thorn was the first to report the clinical effect of an intra-articular injection with 10 mg hydrocortisone in an inflamed knee joint of a RA patient (51). The knee improved locally, but the patient also showed a general improvement, and it was concluded that the beneficial effect resulted from systemic absorption of the steroid.

Early studies demonstrated that hydrocortisone, the natural hormone, was too water soluble, was dispersing too quickly, and was too easy to break down, to produce a long-lasting effect locally (52, 53). New synthetic preparations with branched and chained esterforms in microchrystalline structures were therefore developed (Figure 1-3). They had higher molecular weight, were slower to break down and released the active substances during a prolonged period (54). Furthermore, the synthetic derivatives were more potent than the natural hormone (55).

Figure 1. Trimacinolone Hexacetonide

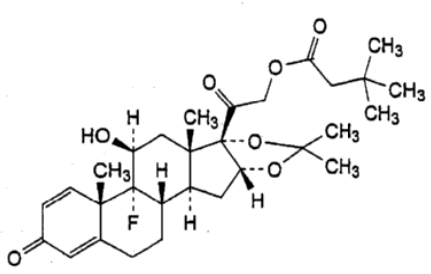


Figure 2. Triamcinolone Acetonide

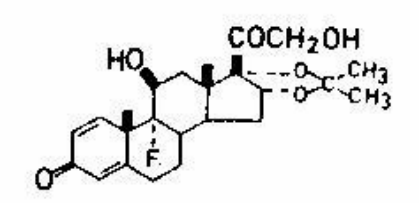
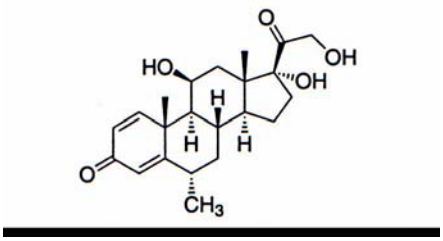


Figure 3. Methylprednisolone



The active substance stayed longer in the joint and had less systemic effects. It is generally believed that most of the injected corticosteroid disappears from the synovial fluid within hours, probably by synovial cell endocytosis and digestion in the acidic environment of the lysosome (56). However, the metabolites can remain in the synovial lining cells for several weeks (57).

The most used long-acting preparations in the US are methylprednisolone (MP), triamcinolone acetonide (TA) and triamcinolone hexacetonide (THA) (58). Interestingly, TA is an active metabolite to THA (59). See Figure 1-3. Comparative studies have shown a more long-acting effect of THA than of MP (60-62) and TA (63-66), but no studies comparing MP and TA have been published. The median duration of improvement after injection of the rheumatoid knee with THA varies between 13 (62) and 21 weeks (67). The local clinical response for knee injections with 20 and 40 mg THA is in the same magnitude (62).

The exact mechanism of the anti-inflammatory action is not fully understood, but it probably includes inhibition of inflammatory mediators like prostaglandins and cytokines (TNF-α, IL-1 and IL- 6), as well as several cellular functions in the immune system. THA has been shown to inhibit the expression of genes for collagenase, human leukocyte antigen (HLA)-DR, tissue inhibitor of metalloproteinases and complement components C2 and C3 in RA patients following knee injection (68). Intra-articular administration of THA also down-regulates the adhesion molecule ICAM-1, a mechanism which may contribute to the reduction of T cells in the synovial membrane (69).

The short term clinical response is very impressive, with reduction within hours or days of inflammatory signs and symptoms, such as heat, pain, swelling and effusion. Magnetic resonance imaging (MRI) has confirmed the reduction of the pannus and the inflammatory synovial volume after intra-articular corticosteroid treatment in the knee (70).

Some authors suggest that the anti-inflammatory effect of the injection can be used as an instrument in diagnosing inflammatory joint disease (57). However, intra-articular corticosteroids may even be helpful in advanced destructive arthritis, when symptoms are caused by mechanical synovitis and joint debris rather than immunological processes.

When the swelling and pain are reduced after injection treatment, the muscle strength and mobility of the joint may be restored. Preserving the joint function is a main goal in the treatment of arthritis.

The following indications for intra-articular glucocorticoid therapy have been suggested (56):

1. To “debulk” the total pool of inflamed synovium in a patient with uncontrolled RA.
2. To correct flexion contractures of large joints.
3. To control inflammation in joints failing to respond adequately to DMARD therapy.
4. As definitive treatment for patients with relatively few joints involved to obviate the risk for systemic drug therapy.

The injection procedure

In addition to the choice of corticosteroid preparation (discussed above), several other factors are possible predictors of a good treatment response. Disease activity and degree of joint destruction have been assumed to influence the efficacy of the steroid injection, but so far it has not been shown that these factors do influence the outcome (71, 72). Neither disease duration, radiological scores, joint counts nor blood levels of inflammatory parameters, such as erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP), correlate with the efficacy of intra-articular steroids in adults. Only a high percentage of synovial fluid polymorphonuclear leukocytes seem to relate to better treatment results (71). Recently it has been reported that children with juvenile idiopathic arthritis and who have a high ESR, are more likely to benefit from intra-articular injection of the knee (73).

In contrast, a correct placement of the injection needle seems to be important for the outcome. This is supported by the results of a clinical injection study of inflammatory pain conditions in the shoulder (74). However, a surprisingly high frequency of incorrect injection placement has been demonstrated (75). Despite that the injections in that investigation were performed by experienced physicians, a large proportion of the injections were shown to be extra-articular. Barely 50% of the injections were proven to be strictly intra-articular, whereas 29% were definitely extra-articular. Aspiration of synovial fluid was associated with a correct placement of the needle. The authors also commented that deposition of steroid outside the joint lead to a reduced clinical response rate. In another study using mini air-arthrography it was shown that 9% of knee joint injections were extra-

articular (76). Ultrasound has therefore emerged as a valuable technical support for accurate injection placement (77). In the future, MRI could also be a possible way to improve the injection technique, but availability and costs are limiting factors.

The injection procedure itself may also contribute to the beneficial effect of the intra-articular glucocorticoid treatment, because an invasive therapeutic procedure may have powerful additional placebo effects (78).

The routines for the injection procedure vary between physicians, for instance concerning synovial fluid aspiration before the corticosteroid is injected. In the literature there are diverging opinions on the importance of arthrocentesis and the reason for this divergence may be related to a lack of scientific studies.

Neustadt recommend aspiration of as much synovial fluid as possible in order to reduce the intra-articular pressure, to decrease the potentially deleterious effects of destructive enzymes in the synovial fluid, and to diminish the dilution of the injected corticosteroid (67). In contrast, Williams and Gumpel suggest that there should be synovial fluid left in the joint, so as to permit free diffusion of steroid in the joint cavity (79). Dixon and Emery also recommend aspiration, because their experiences are that arthrocentesis may give a more immediate reduction of pain and that the steroid effect may appear earlier (55).

A complete aspiration of synovial fluid is time consuming and if it does not influence the treatment result, it might be excluded. As intra-articular glucocorticoid treatment is used in everyday practice, this is a question that needs to be answered.

The importance of post-injection rest

In studies when radioactive yttrium and gold have been injected in knees of mobile patients, a significant leakage of these substances into inguinal lymph nodes and liver has been found. Such leakage could not be demonstrated in resting patients (80-83). After these observations, the recommendation of a 24-48 hour post-injection bed rest after intra-articular glucocorticoid treatment, has been introduced. A hypothesis that motion, loading, and high intra-articular pressure may increase the absorption of the drug from the joint to the general circulation has been postulated (67). Consequently, in mobile patients the local treatment response should decrease.

The issue of whether to rest or immobilize every injected joint after intra-articular corticosteroid treatment is controversial. Most rheumatologists advise their patients not to use the joints for a period of time after injection (84-85), but some authors consider the evidence for using this routine is not convincing (86). Also the length of the recommended resting period varies. Most physicians recommend 24-48 hour post-injection rest, because a very

long immobilisation period may lead to joint stiffness, muscular hypotrophy, weakness and reduced coordination capacity (87). A recent Cochrane review reported almost a complete lack of concordance among practitioners regarding the procedures of intra-articular injections, including the use of rest or post-injection splints (88).

The effect of rest on small hand joints injected and placed in a resting splint for three weeks has been studied in twelve RA patients and a prolonged therapeutic effect in the splinted joints was reported (89). The rationale for the long post-injection rest period in this study was to minimize the leakage of steroid chrystals back through the needle track, as well as to provide time for repair of the tissue damage that may be caused by the inflammatory process.

Investigations demonstrating better treatment results of intra-articular steroid injections for knee synovitis, if followed by 24-48 hour post-injection bed-rest (67, 90) support the hypothesis that immobilization retards glucocorticoid resorption. However, in another study no increased therapeutic effect of 48 hour rest after intra-articular glucocorticoid treatment could be demonstrated. In the investigation, weight-bearing and non weight-bearing joints were mixed, making it difficult to draw firm conclusions (91). The result suggests that immobilisation of the non weight-bearing joints could be less important. It is important to answer this question in order to provide adequate recommendations to the patients after the treatment, but the issue has not been studied systematically.

Effects on cartilage metabolism

Early observations suggested that frequent intra-articular glucocorticoid injections caused destructive joint changes (92, 93). Charcot-like arthropathy was considered a serious adverse reaction to intra-articular glucocorticoid administration. However, this conclusion has been disputed because a need for repeated injections also indicates a therapy-resistant synovitis within the joint. Therefore, the synovitis itself could be a more likely cause of joint destruction than the glucocorticoid injection (94).

Support for a destructive role of intra-articular glucocorticoids was given by the findings in several studies on rabbits and rats. They have shown that intra-articular corticosteroids impair cartilage metabolism. Loss of chondrocytes and reduction of proteoglycan synthesis have been observed (93, 95). This caused matrix degradation as revealed by the loss of proteoglycans. The combination of exercise and repeated hydrocortisone injections in rats lead to even more cartilage damage than the injections alone (96).

In contrast, investigations on primates (97) and dogs (98) have not revealed histological lesions in normal articular cartilage when exposed to intra-articular corticosteroids.

Furthermore, intra-articular steroid injections may prevent cartilage damage in experimental osteoarthritis (OA) (98-100). Consequently, corticosteroids may have chondroprotective properties in joint disease.

The conflicting results may depend on the different species studied. Therefore, effects of intra-articular glucocorticoid injections on healthy animal joints may not reflect the effects in human joints, and certainly not in human arthritis.

Adding low dose oral corticosteroids to methotrexate treatment may prevent the progress of joint erosions in RA patients (101, 102). It is not yet known if similar joint protection can be obtained with intra-articular administration. A randomised and controlled study with both more intense intra-articular glucocorticoid therapy and DMARD therapy showed a nonsignificant reduction of the radiological joint erosions compared with the control group (103)**.**

Biochemical markers of cartilage degradation have been defined and methods have been developed to analyze these in serum samples. Cartilage oligomeric matrix protein (COMP) is an extra-cellular glycoprotein synthesized by both chondrocytes and to a small extent in synovial cells (104). COMP binds to collagen type II and is considered to be important for fibril formatting and stabilisation of the collagen network (105). The levels are elevated in serum of patients with OA (106) and RA, but in unselected RA-patients they show a wide range, probably depending on both the grade of articular involvement and the grade of remaining cartilage. In arthritis, elevated serum COMP levels reflect more the structural deterioration than the inflammatory process in the joints (107, 108). Low dose oral prednisolone treatment as well as intra-muscular administration of MP has been shown to decrease s-COMP (109).

If glucocorticoids are retained in the joint after intra-articular injections with immobilization, there could be enhanced glucocorticoid effects within the joint. This should influence the anti-inflammatory effects on the synovial membrane as well as the cartilage metabolism. The influence on serum levels of cartilage degradation markers, such as proteoglycans and COMP, by intra-articular glucocorticoids in RA is not known. The effects on the different markers can provide new and valuable information about the consequences for the cartilage of this very common therapeutic method.

Effects on bone metabolism

Treatment with systemic glucocorticoids influences the bone metabolism and in the long term secondary osteoporosis may be induced (110, 111). The

mechanism is not fully understood, but seems to be multi-factorial. The production of sex hormones, such as estrogen and testosterone, is decreased. Bone formatting osteoblasts are suppressed (112) and the apoptosis is increased. Reduced intestinal calcium absorption, increased renal calcium excretion, and a secondary hyperparathyroidism are also important factors in the process (110). If intra-articular glucocorticoid injections are repeated too often, a secondary steroid induced osteoporosis may be expected also with this intermittent administration route.

The bone mass is the net result of two opposing metabolic processes: the bone formation by osteoblastic cells and the bone resorption by osteoclastic cells. Under normal conditions the processes are coupled to each other. Biomarkers of bone metabolism are useful in order to detect imbalances in the dynamics of the bone turn over,

Bone formation

Bone-specific alkaline phosphatase (BAP) and osteocalcin are proteins produced by the osteoblastic cells and they are the most commonly used markers of bone formation (112). They reflect different stages in the osteoblastic cell differentiation. BAP is mostly produced by mature osteoblasts and osteocalcin is produced during the late mineralization phase (2).

BAP is a membrane bound enzyme located on the outer cell surface. The precise function is not yet known, but it may play an important role in osteoid formation and mineralization.

Osteocalcin is the most abundant non-collagenous protein in the bone matrix, has calcium-binding properties, and is assumed to be involved in the mineralization process (112).

Bone resorption

Collagen type I is the most common collagen of the bone matrix (2). The type I collagen molecules are linked together by cross-linking molecules such as pyridinoline and deoxypyridinoline. The former is also present in cartilage because the different and cartilage-specific type II collagen molecules are covalently linked by pyridinoline. Deoxypyridinoline is a more bone specific marker, as measured in urine, and provides a sensitive index of bone resorption in RA (113).

Bone metabolism and intra-articular glucocorticoid treatment

A single intra-articular injection of 40 mg TA in RA patients reduced the serum levels of osteocalcin during a two week period after the injection (114), but no significant changes of urinary pyridinolin was seen. This result suggested a transient systemic effect on the bone formation. The joints in the study were kept in “relative” rest for 48 hours after the injection.

The inflammatory processes as well as the immobilisation procedure and changes in the glucocorticoid resorption are factors that all may influence

bone metabolism after intra-articular treatment. The net result on bone is not easily predicted, but could be clarified by using serum markers of bone turnover.

Effects on the HPA-axis

The systemic absorption of intra-articular corticosteroids may influence the cortisol metabolism by suppressing the HPA-axis via negative feedback mechanisms. Depending on the preparation chosen, the dose, and how often the injections are repeated, long-term side effects might also be expected. In fact, a few cases with adrenal insufficiency after frequently repeated intra-articular glucocorticoid injections have been reported (115).

It has been demonstrated that the absorption of different glucocorticoid suspensions from knee joints is complete after a period of 2-3 weeks (59). After intra-articular injection with MP, the serum peak concentration of the substance appeared 2-12 hours later (116). Interestingly, there was more systemic absorption when giving 40 mg MP in both knees, than giving 80 mg in one. It was suggested that the total area of inflamed synovium, would determine the degree of absorption. This conclusion is supported by another report showing more systemic corticosteroid resorption after intra-articular injections in inflamed knees than in knees without signs of synovitis (117).

After injections with 80 mg MP in knee joints, plasma cortisol levels are reduced for up to one week (116, 118, 119). A suppression of the HPA-axis, measured as a weak stress-response to insulin induced hypoglycemia, has also been observed (118). In a comparison between different glucocorticoid suspensions, THA had the weakest suppression of endogenous hydrocortisone production. The suppression was maximal after one day and normalised after 9 days on 20 mg THA (59). Cortisol levels in saliva of children were suppressed during 10-30 days after intra-articular steroid therapy for knee synovitis with THA 1 mg/kg body weight (20-60 mg). However, the doses per kg body weight were much larger than used in adults (120).

If joint immobilisation can reduce the systemic steroid resorption capacity in the synovium, the systemic side effects in the HPA-axis could also be influenced. However, in the published studies information about the post-injection regimen is often missing (59, 120, 121). When reported, the length of the resting period varies considerably, from a few hours (118) up to a whole week (116). It seems that the possibility of significant differences in glucocorticoid resorption has not been taken into account. The relation between joint rest, glucocorticoid resorption and the resulting influence on the HPA-axis needs to be better elucidated.

Complications

Intra-articular glucocorticoid treatment is generally regarded as a safe method to relieve signs and symptoms of arthritis. However, in addition to the previously discussed metabolic consequences, local complications have also been reported.

When corticosteroid suspension leaks into the injection canal, benign soft tissue atrophy may follow (122). Incidence figures vary between 0 and 14 % (123) and it usually appears 4-22 weeks after the injection (122, 124). The small interphalangeal joints of the fingers seem to be the most susceptible.

Occasionally periarticular calcifications are seen on radiographs. They are completely asymptomatic and seem to be related to the site of needle perforation (125).

Ligaments and joint capsules may be distended during joint inflammation. Pain and stiffness may lead to disuse of the joint and reduction of muscle strength. Therefore, when the anti-inflammatory effect of the glucocorticoid treatment appears, a joint instability may follow. In early studies of intra-articular injections, this side effect was reported in 5 % of cases (126).

Post-injection flare occasionally occurs. It is an increase in the local inflammation, which may develop a few hours after injection and last up to 48 hours. An incidence of 1-2 % has been reported (126). The reaction was more common when using earlier steroid preparations, but it has also been reported with THA (127). It may be a form of chrystal-induced arthritis produced by synovial fluid leukocytes phagocytosing the chrystals and subsequently releasing lysosomal enzymes (127, 128). It can sometimes be difficult to distinguish the post-injection flare from a joint infection.

Bacterial arthritis is the most feared complication following injection therapy and may cause severe damage to the affected joint or even death in septikemia. Fortunately, this complication is reported to be very rare. Studies have estimated the incidence to 1/10,000-1/16,000 injections (129, 130). Patients with high age, immunosuppressive disorders or treatments seem to be the most susceptible. Staphylococcus aureus is reported to be the most common microbial agent (131, 132).

An antiseptic injection technique is crucial in order to avoid infectious complications, but the trend seems to be towards reducing the number of sterile precautions (133). The optimal technique is unknown and there is a considerable variation in practice and no good data on the need for sterile precautions to prevent post-injection infection (134). Sterile gloves were used by 50 % of Swedish rheumatologists (85), to be compared with 32% in the UK (133) and 25% in the US (135).

Perforation with the injection needle through a skin infection may lead to bacterial contamination of the treated joint. This is to be especially remem-

bered when treating patients with psoriatic arthritis with severe skin manifestations.

The occurrence and the characteristics of bacterial arthritis following intra-articular injections in this part of Sweden have not been investigated before. Such a study can provide valuable information about the safety and the quality of the injection routines.

PRESENT INVESTIGATIONS

Aims

The general aim of this thesis was to find ways to make the intra-articular glucocorticoid injection procedure more optimal with a maximum of efficacy and safety. More specifically, the aims were:

- To study if synovial fluid aspiration in the intra-articular corticosteroid procedure influences the duration of treatment response for knee synovitis.

- To study if post-injection immobilisation of the wrist influences the efficacy of intra-articular glucocorticoid therapy.

- To the study influence on markers of bone and cartilage turnover after intra-articular corticosteroid injection of the knee in mobile and resting patients with rheumatoid arthritis.

- To study glucocorticoid resorption and the resulting influence on the HPA-axis after intra-articular corticosteroid injection of the knee in mobile and resting patients with rheumatoid arthritis.

- To study occurrence, characteristics, and outcome of bacterial arthritis, with particular reference to infections following intra-articular corticosteroid injections.

Methods and Results

Paper I

In this prospective randomised and controlled study on the importance of synovial fluid aspiration, a total of 191 knees on 147 patients with RA and a symptomatic knee effusion were included. All patients were treated with an intra-articular injection with 20 mg THA. They were randomised to either a complete aspiration of synovial fluid before the injection (n=95) or a THA injection without previous aspiration (n=96). All patients were recommended a 24-hour post-injection rest at home. The relapse rate was followed for six months.

The patients were told to contact the Department of Rheumatology if symptoms from the treated knee recurred. If a relapse was suspected the knee was re-examined and if there were clinical signs of synovitis, a relapse was recorded and the patient was offered another injection. Most patients were followed at regular visits at the outpatient clinic, but otherwise phone-calls were made after six months to confirm that no unknown relapse had occurred.

The results showed that the proportion of relapses in the aspiration group during the observation period was significantly reduced (p=0.0009). At the end of the study there were 23% relapses in the aspiration group and 47% in the no aspiration group (p=0.001). The absolute risk reduction was 24% and the number of patients needed to treat (NNT) to avoid one relapse was 4.2.

Paper II

A prospective randomised controlled study was designed to evaluate the importance of post-injection rest for wrist synovitis.

A total of 117 consecutive patients with RA and wrist synovitis were included. The patients were randomised to 48-hour post-injection rest (n=58) in elastic wrist orthoses (Elcross Carpi Flexi, Camp Scandinavia) or to normal activity (n=59) after intra-articular wrist injection with 10 mg THA. The patients were followed for six months.

The primary endpoint was relapse of synovitis. As in Study I, the patients were told to contact the Department of Rheumatology if symptoms from the treated wrist recurred. When that happened the wrist was re-examined and if there were clinical signs of synovitis, a relapse was recorded and the patient was offered another injection.

Furthermore, a number of secondary parameters were measured before treatment and after one week, three months and six months. Grip strength was measured electronically with a Grippit instrument (136, 137). To assess

pain and function, the patient-rated wrist evaluation (PRWE) (138, 139) was used. This is a standardised, reliable and validated self-administered questionnaire designed to evaluate wrist pain and disability. Wrist joint circumference and maximal range of active movement were also followed.

The results showed a trend to more relapses in the immobilisation group ($p=0.0694$). During the study there were 24 relapses (41%) in the orthoses group and 14 relapses (24%) in the group with normal post-injection activity ($p=0.056$). The absolute risk reduction was 17%.

The changes of the secondary parameters showed no significant differences between the groups after one week, three months and six months.

Paper III and IV

An open prospective randomised controlled trial was designed to evaluate the effect of intra-articular glucocorticoid administration on hormones of the HPA-axis and on markers of bone and cartilage turnover.

Twenty consecutive patients with RA and synovitis of the knee were enrolled. The patients should not have been exposed to systemic glucocorticoid treatment the last year and not to intra-articular glucocorticoids the last two months. Ten patients had a 24-hour post-injection bed rest supervised at the hospital and ten were mobile with no restrictions.

All patients were treated with an intra-articular injection of 20 mg THA at 8 hours a.m. A 24-hour urine sample of cortisol was collected the day before and the day after the injection. To assess the influence on hormones of the HPA-axis, serum samples of cortisol and ACTH were collected just before the injection and after 24 and 48 hours. Samples were also taken after seven and fourteen days.

At the same time serum samples were collected for COMP to evaluate the influence on cartilage degradation, for osteocalcin to evaluate the influence on the bone formation, and urine samples for deoxypyridinoline to determine the rate of bone degradation. Serum samples of THA were assessed at 8 hours, 24 hours, 48 hours as well as day 7 and 14.

COMP was also analyzed in synovial fluid aspirated at the time of injection. Within six weeks all patients had a radiological examination of the knee.

The results showed that the serum levels of COMP decreased within 24 hours ($p<0.001$) in both patient groups. The decrease was significantly more pronounced in resting patients ($p=0.007$). After one week, the serum COMP level in mobile patients was no longer decreased compared with baseline. In the resting patients, on the other hand, significantly decreased levels were noted throughout the study.

Osteocalcin decreased within 24 h in both groups ($p<0,001$), and there was no difference between resting and mobile patients. In mobile individuals significantly reduced levels could be seen for 48 h and in resting patients

during the first week. Deoxypyridinoline, the marker of bone resorption, was unaffected in both groups.

There were significant and reversible decreases in serum cortisol and ACTH levels ($p<0.001$) without any significant differences between resting and mobile patients. The THA levels increased similarly in both groups and the peak concentration occurred after 8 hours.

Paper V

At the Departments of Infectious Diseases, Orthopedic Surgery and Internal Medicine at Gävle Hospital, all cases of culture verified infectious arthritis during a four-year period were identified in the registers of diagnosis. The patient records were studied retrospectively and the association to intra-articular injection treatment at the Department of Rheumatology was established. The number of intra-articular corticosteroid injections at the department during the period was calculated from the amount of THA used. There was no THA available during 8 months and MP was used instead. Those injections were not included, since MP was used both for intra-articular and extra-articular injections. This procedure would certify that the calculated number of intra-articular injections was not overestimated.

Information concerning previous medical history, presenting joint, delay between onset of symptoms and diagnosis, presenting symptoms and signs, source of infection, immune suppression, causative organism, results of joint aspiration and haematological indices, treatment, radiological outcome, as well as medical complications and death were also extracted in each case.

During the studied four year period, 15 cases of culture positive infections in native joints were identified, which makes the calculated annual incidence of infectious arthritis in this region to be 4.1/100 00 inhabitants.

The knee was the most frequently affected joint. Staphylococcus aureus was the most common microbial agent and was also the pathogen in the most severe cases - in two patients causing death.

Direct inoculation was seen in six patients. Only one of them had been treated with intra-articular glucocorticoids. The patient had a severe RA with renal insufficiency and had an injection in his right shoulder performed at the Department of Rheumatology. During the observation period at least 12,000 injections were performed at the department.

Statistical methods

When comparing patient characteristics between the treatment groups at base line, Students T-test, χ^2-test or Mann Whitney U-test was used when appropriate. Log rank test was used in Study I and Study II to calculate differences in survival rates between the groups. χ^2-test was used to compare propor-

tions of relapse at the end of the observation periods. Analysis of covariance with baseline as covariate was used when comparing the treatment groups regarding repeated wrist measurements in Study II, repeated values of markers for bone and cartilage turnover in Study III, and for repeated values of hormones in Study IV. For comparisons within groups one sample T-test was used. Mann-Whitney U test was used when comparing the levels of resorbed THA between the groups in Study IV.

DISCUSSION

There is a new era in clinical rheumatology and more effective treatment options are available today. With increasing knowledge of arthritis immunology, the development of biological preparations, such as TNF-α blockers, has been possible. Many of the old treatment regimens will probably be sorted out because of inefficacy or of risk for unacceptable adverse reactions. However, there will always be some patients with inadequate treatment response. Relapse of arthritis will sometimes occur and therefore intra-articular glucocorticoid injection treatment will remain an important tool in the therapy of arthritis.

In situations when few joints are affected with synovitis the glucocorticoid injection has many advantages, compared with treatment with NSAID. In addition to lower costs, the treatment gives a more long-lasting and rapid pain relief with a lower risk for serious side effects. Infectious complications are very rare. In this material (Study V) there was less than one infection per 12,000 injections.

In this thesis the expected outcome for intra-articular glucocorticoid therapy in RA, measured as the duration of clinical response, has been investigated for injections in both knees and wrists. In the present studies, as many as 77% of the patients with knee injections (Study I) and 76% with wrist injections (Study II) had an adequate treatment response persisting after six months. The relapse rates for the different joints were surprisingly equal.

Adequate injection routines are important and influence the outcome of intra-articular glucocorticoid therapy. General recommendations for clinical practice should rely as much as possible on evidence from findings in controlled studies. In such guidelines concerning injection routines, recommendations that cause extra costs or discomfort for the patients should be eliminated.

The present controlled investigation (Study I) has shown that synovial fluid aspiration before the steroid is injected reduces the relative risk for relapse of the arthritis by more than 50%. In addition, when the synovial fluid is removed the intra-articular pressure decreases, which causes a rapid reduction of joint pain and a better joint mobility. The arthrocentesis procedure is time consuming but is now shown to be an indispensable part of the intra-articular glucocorticoid treatment.

The underlying mechanism for this effect may be multi-factorial. First of all, the synovial fluid aspiration decreases the intra-articular pressure, which

may prevent synovial hypoxia (1, 7). Secondly, after aspiration the injected glucocorticoid becomes less diluted, which may increase the efficacy. Furthermore, the removal of proinflammatory substances, destructive enzymes, cartilage degradation products, and other antigens that could maintain inflammation is probably another important mechanism. Previous studies have shown that joint lavage is effective in reducing inflammatory signs and symptoms. Therefore, adding joint lavage to intra-articular glucocorticoid therapy may further improve the outcome (140, 141). In conclusion, the findings in the present investigation, together with other studies, indicate that the cleaning process of the joint is important for the treatment result.

Although recommendations of post-injection rest are included in most guidelines for intra-articular injection therapy, some authors have questioned this regimen (86). So far the beneficial effects of rest have only been shown for knee injections. Study II shows that wrists do not respond the same way to immobilisation procedures. The discrepancy may depend on differences in joint size, anatomy, joint mobility or the position for weight-bearing. Furthermore, the glucocorticoid resorption may also be different in the wrist compared with the knee. The area of inflamed synovium is smaller in the wrist and the resorption capacity could be as well.

If all treated patients stay home from work in order to rest the injected joint, the costs for the society would be considerable. Beside the inconvenience for the patient, the cost-benefit analysis would not be favourable.

Study III did not show any difference between resting and mobile patients in regard to the influence on bone metabolism. Bearing in mind that the markers that were used not necessarily reflect long term cell activity, the bone formation seems to be suppressed for one week after injection. In contrast, bone resorption seems to be mainly unaffected. The short-term influence on bone metabolism by intra-articular glucocorticoids may therefore entail a low risk to induce osteoporosis. The intra-articular glucocorticoid injections are in many aspects equal to intermittent intravenous pulse therapy. A recent investigation has shown that glucocorticoid pulse therapy every second month for one year has no negative effect on markers of bone metabolism or bone mineral density in contrast to low dose daily oral glucocorticoids (142). For arthritis patients with severe osteoporosis, intermittent intra-articular treatment may therefore be preferred before low dose oral administration.

In contrast to markers of bone turnover, the marker of cartilage turnover, COMP, is significantly more decreased in the resting patients. This finding supports that the local effect of the injected glucocorticoid is more pronounced in immobilised knees. The result may also suggest that the intra-articular glucocorticoid injection treatment may prevent cartilage destruction. If so, this therapy not only relieves signs and symptoms of arthritis, but may also have chondroprotective properties, which is important for the pres-

ervation of joint integrity and function.

Guidelines for intra-articular glucocorticoid therapy often recommend to avoid injections in the same joint more often than every third month in order to reduce the risk for steroid induced cartilage damage (143, 144). In experimental studies, cartilage degradation after intra-articular glucocorticoid administration in small and healthy animal joints were observed and seemed to support this strategy (93, 95, 96). On the other hand, studies in larger species have shown no deleterious effects (97, 98) and intra-articular corticosteroids may even protect from experimental OA (98). Such chondroprotective effects may possibly be explained by steroid-induced inhibition of metalloproteinase activity (145, 146).

Frequent glucocorticoid injections do not increase the risk for arthroplasty in RA (147). Furthermore, a recent study on patients with OA of the knee and treated with intra-articular glucorticoids every third month for two years could not demonstrate any radiological progress in the treated joints compared with the control group (148). In addition to the findings in Study III, there are more and more observations that support the view that the destructive consequences of arthritis are more harmful for the joint than the possibly degenerative effects of the injected glucocorticoid. Early arthritis relapse causes pain and disuse of the affected joint, which may cause muscle weakness and joint instability if untreated. To deny a suffering patient a glucocorticoid injection because the interval to the latest injection is too short seems unethical and should be regarded as malpractice.

If there is a need for injection treatment very frequently, however, one should consider other explanations for early arthritis relapse, such as persisting mechanical problem, low virulent joint infection, uncontrolled general disease activity, or inaccurate injection placement.

Finally, Study IV cannot confirm any decreased serum THA levels after intra-articular administration in patients with post-injection rest compared with mobile patients. Accordingly, the degree of suppression of the HPA axis does not differ between the resting and mobile patients. The suppression is of short duration and reversible. Normalization of cortisol levels occurred within two weeks and ACTH levels within two days after injection. Taken all the findings together there is no support for retarded glucocorticoid resorption in patients with post-injection rest, because serum levels of the injected THA as well as the systemic side effects in the HPA-axis and bone are equal in resting and mobile patients (Study III and IV). The established clinical truth that post-injection rest reduces glucocorticoid resorption from the joint should therefore be revised. Other explanations for the improved outcome of intra-articular glucocorticoid treatment for knee synovitis in patients with bedrest must be considered and will be an important task for future research.

Earlier recommendations for injection treatment, of which many have never been confirmed in studies, may be considered old-fashioned in a time when reducing costs and saving time are given a high priority. Most physicians nowadays have injection experiences of their own and, as there has been a lack of evidence-based knowledge, many different routines based on private opinions, have been developed.

The results of the studies included in this thesis should therefore be a valuable contribution to the knowledge about intra-articular glucocorticoid treatment. The importance of synovial fluid aspiration for a good treatment response should be emphasised (Study I). Immobilisation after knee injections should still be recommended, but not for wrists according to Study II. The fear for cartilage damage (Study III) or infections (Study V) induced by intra-articular injections seems to be exaggerated.

The findings may hopefully stimulate general practitioners and specialists to review their injection routines. The well known but inappropriate differences in recommendations can hopefully be reduced when new guidelines for the clinical practice are made.

One step closer to concordance would thereby be taken.

CONCLUSIONS

- Synovial fluid aspiration before injecting intra-articular glucocorticoid in the knee reduces the risk for arthritis relapse and should therefore be a part of the injection procedure.

- In contrast to what was expected from previous studies on knees, immobilisation after intra-articular glucocorticoid therapy for wrist synovitis does not improve the outcome and should not be recommended. Findings in knee studies can not be applied to all joints.

- The reduction of serum COMP after intra-articular glucorticoid injections in knees may suggest that the treatment is chondroprotective. The pronounced reduction in resting patients suggests increased local treatment response in this group.

- The intra-articular glucocorticoid injection has a short term and reversible influence on bone metabolism. Bone formation is decreased independently of the immobilisation procedure. Bone resorption is unaffected after the injection.

- In resting and mobile patients, the short term and reversible suppression of the HPA-axis is similar after intra-articular glucocorticoid administration.

- The serum THA levels after intra-articular administration are similar in resting and mobile patients indicating that the mechanism for improved outcome of post-injection rest for knee synovitis not is delayed or reduced systemic resorption of the drug.

- Infectious complications after intra-articular injection treatment are very rare, less than 1/12,000 injections in this material.

SUMMARY IN SWEDISH

Vid behandling av reumatiska ledsjukdomar är det vanligt att en injektion med kortison ges direkt i den inflammerade leden. Det är ett effektivt sätt att lindra reumatiska ledsymptom, såsom värk och svullnad.

Injektionsrutiner varierar emellertid avsevärt mellan olika läkare. Det råder till exempel oenighet när det gäller om leden ska tömmas på ledvätska eller inte vid injektionsbehandlingen. I denna randomiserade och kontrollerade undersökning (Studie I) på patienter med ledgångsreumatism visade det sig att risken för återfall av knäledsinflammation minskade påtagligt när leden tömdes på ledvätska vid injektionen.

Det råder inte heller någon enighet när det gäller vilka behandlingsråd som ska ges efter injektionen. Tidigare studier har visat bättre behandlingseffekt när en knäled behandlad med en kortisoninjektion avlastas 1-2 dygn efteråt, men många rekommenderar vila också efter kortisoninjektion i andra leder. I den randomiserade och kontrollerade Studie II kunde emellertid inte visas någon gynnsam effekt av att immobilisera handleder i handledsstöd under 48 timmar efter injektionen. Detta visar att andra leder kan reagera annorlunda och att vila efter ledinjektioner inte alltid bör rekommenderas.

Det förbättrade behandlingsresultat som noterats av att vila efter knäledsinjektioner har antagits bero på fördröjd eller minskad resorption av kortisonet från leden ut till blodcirkulationen. För att belysa detta analyserades serumnivåer av den använda steroiden, triamcinolon hexacetonid (THA), dess påverkan på ämnesomsättningen i brosk och ben samt på kroppsegen kortisonproduktion i den s.k. HPA-axeln (Studie III och IV). Blodprover togs under en tvåveckorsperiod efter kortisonbehandling av en knäledsinflammation hos både vilande och uppegående patienter med ledgångsreumatism. För att värdera hormonproduktionen i HPA-axeln analyserades cortisol och ACTH. Cartilage oligomeric matrix protein (COMP) användes som markör för broskpåverkan, osteocalcin som markör för benuppbyggnad och deoxypyridinolin som markör för benresorption.

Resultaten visade en kortvarig och övergående dämpning av HPA-axeln och benuppbyggnaden, medan benresorptionen inte alls påverkades av kortisoninjektionen. Det fanns ingen påvisbar skillnad mellan vilande och uppegående patienter. COMP nivåerna sjönk påtagligt i båda grupperna, men

mest i vilogruppen. Detta kan tala för en broskskyddande effekt av kortisoninjektionen och att vila förstärker den lokala behandlingseffekten. THA nivåerna ökade på likartat sätt i båda grupperna, vilket tyder på att vila inte fördröjer eller minskar kortisonresorptionen från leden efter en knäledsinjektion. Den vedertagna förklaringen till förbättrade behandlingsresultat vid vila bör således omprövas.

Den allvarligaste komplikationen till behandling med kortison i inflammerade leder är infektion i den injicerade leden, vilket lyckligtvis är ovanligt. I detta material (Studie V) var förekomsten mindre än en gång på 12000 ledinjektioner.

Resultaten i detta arbete kan direkt överföras till den kliniska vardagen och bör därför hållas i åtanke när råd och rekommendationer för injektionsbehandling av inflammerade leder ska ges.

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