CONCISE REPORT

Glucocorticoid resorption and influence on the hypothalamic-pituitary-adrenal axis after intra-articular treatment of the knee in resting and mobile patients

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Background: Studies have shown that intra-articular glucocorticoid injection treatment for knee synovitis has a better outcome in resting patients than in mobile patients. One reason for this observation might be that rest retards steroid resorption, causing an enhanced local treatment effect.

Objectives: To study drug resorption and the impact on hormone production in the hypothalamic-pituitary-adrenal axis after intra-articular glucocorticoid administration, with and without postinjection rest.

Methods: Twenty patients with rheumatoid arthritis and knee synovitis were randomised to either 24 hour bed rest or normal activity after intra-articular glucocorticoid treatment with 20 mg triamcinolone hexacetonide (THA). Serum levels of THA, cortisol, and adrenocorticotrophic hormone (ACTH) were followed during 2 weeks.

Results: Short term and reversible decreases in serum cortisol and ACTH levels ($p < 0.001$) were seen, without any significant differences between resting and mobile patients. The THA levels increased similarly in both groups, with the median serum peak seen after 8 hours.

Conclusion: Immobilisation does not appear to retard glucocorticoid resorption after intra-articular administration. Further studies are therefore needed to clarify the mechanism behind the beneficial effects of rest after intra-articular glucocorticoid treatment for knee synovitis.

Studies have shown that intra-articular (IA) glucocorticoid treatment for knee synovitis has a better outcome if followed by 24–48 hours' postinjection rest.^{1,2} One possible explanation for this observation is that the immobilisation increases retention of glucocorticoid deposition in the joint, resulting not only in increased local therapeutic effect but also reduced systemic absorption.² If this assumption is correct, the systemic side effects of the IA glucocorticoids should be reduced in patients immobilised after the injection. To clarify if there is any difference in drug resorption in mobilised versus immobilised patients after IA glucocorticoid treatment, we examined serum triamcinolone hexacetonide (THA) levels and the effects on the hypothalamic-pituitary-adrenal (HPA) axis in mobilised and resting patients after IA THA treatment.

PATIENTS AND METHODS

At our outpatient rheumatology departments in Gävle and Uppsala, a total of 20 consecutive patients with rheumatoid arthritis³ and clinical signs of knee synovitis were recruited. The patients were randomly allocated to 24 hours' postinjection bed rest supervised in hospital ($n = 10$) or to normal activity without restrictions ($n = 10$). Patients treated with tumour

necrosis factor blockers, systemic glucocorticoids during the past year, an intra-articular glucocorticoid injection in the knee during the past 6 months, or those with any intra-articular injection in the past 2 months were excluded, as well as patients in functional class 4 according to Steinbrocker.⁴

We used the Swedish version of the Health Assessment Questionnaire (HAQ) to evaluate the level of disability.⁵ General disease activity was assessed with the 28 joint count Disease Activity Score (DAS28) index.⁶ All patients underwent a radiological examination of the treated knee. The radiographs were graded by an independent radiologist according to Larsen-Dale.⁷ No significant differences were found between the groups at baseline (table 1).

After arthrocentesis, 20 mg THA (Lederspan) was injected into the affected knee. All treated knee joints improved after the injection. Serum samples of THA, cortisol, and adrenocorticotrophic hormone (ACTH) were drawn immediately before the injection, and after 24 hours, 48 hours, 1 week, and 2 weeks after the injection. All injections were performed at 8 am and samples were collected at this time on every occasion. An extra THA sample was drawn 8 hours after injection.

To assess the influence on the HPA axis, a 24 hour urine sample of cortisol was collected the day before and the day after the glucocorticoid injection. The 24 hour urine collection failed in one case in the mobile group.

The study was approved by the Committee of Ethics, Faculty of Medicine, Uppsala University, and informed consent was obtained from all patients.

Laboratory methods

The samples were centrifuged for 10 minutes at 1800 *g* within 1 hour and stored at -70°C until all samples had been collected and laboratory processing could be performed.

THA was analysed using liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS in this order) detection⁸ (BEK-analys, Haninge, Sweden). Cortisol was analysed on an Advia Centaur (Bayer Corp, Tarrytown, NY, USA). ACTH measurements were performed by Nichols Advantage (Nichols Institute Diagnostics, San Clemente CA, USA). All laboratory testing was performed without any knowledge of the clinical data or the study group to which the patients belonged.

Statistical calculations

To test for significant differences of the changes in levels of cortisol and ACTH between the groups, analysis of covariance with baseline as covariate was used. For comparisons of changes within the groups, a one sample *t* test was used. All

Abbreviations: ACTH, adrenocorticotrophic hormone; DAS28, 28 joint count Disease Activity Score; HAQ, Health Assessment Questionnaire; HPA, hypothalamic-pituitary-adrenal; IA, intra-articular; THA, triamcinolone hexacetonide

Table 1 Patient characteristics

Characteristics	Rest group (n = 10)	Mobile group (n = 10)	
Female/male (n)	10/0	9/1	
Age (years)*	62 (37–75)	59 (30–76)	NS
Disease duration (years)*	10 (0–53)	14.5 (2–48)	NS
HAQ*	1.2 (0.88–1.63)	1.2 (0.5–2.13)	NS
DAS28*	4.88 (2.79–5.76)	4.99 (3.3–6.4)	NS
Larsen-Dale score†	1.5 (0–4)	1.5 (0–5)	NS

Results are shown as median (range).

*Student's *t* test; †Mann-Whitney U test.

tests were two tailed. To test for differences of serum levels of THA between the groups a Mann-Whitney U test was used. A *p* value <0.05 was considered significant. Statistical analyses were made by the statistical computer software program SPSS, version 11.5 for Windows NT.

Figure 1 Mean levels of serum THA for mobile patients (broken line, empty circles) and patients with 24 hours' postinjection rest (solid line, filled circles) during a 2 week period after intra-articular glucocorticoid treatment for knee synovitis. The results are the mean (SEM) of 10 samples in each group.

Figure 2 Mean levels of serum cortisol (fig 2A) and serum ACTH (fig 2B) for mobile patients (broken line, empty circles) and patients with 24 hours' postinjection rest (solid line, filled circles) during a 2 week period after intra-articular glucocorticoid treatment for knee synovitis. The results are the mean values (SEM) of 10 samples in each group.

RESULTS

The median serum THA peak appeared 8 hours after the injection in both patient groups. For one patient in each group, the peak THA level was reached after 24 hours. For one mobile and two resting patients the peak appeared after 48 hours (fig 1).

The day after the injection, a significant mean (SD) decrease of 24 hour urine cortisol levels ($p < 0.001$) was seen in both treatment groups—in the mobile patients from 7.8 (2.8) to 4.3 (2.1) nmol/h and in the resting patients from 8.4 (2.9) to 5.0 (1.8) nmol/h. In both groups a significant decrease of serum cortisol compared with baseline levels was seen. The lowest levels appeared 24 hours after injection ($p < 0.001$), and were normalised at day 7 in mobile patients and within 2 weeks in resting patients (fig 2A). However, there were no significant differences between the resting and the mobile patients at any time point.

Serum ACTH levels were significantly decreased in both groups ($p < 0.001$). Compared with baseline, the serum ACTH levels were reversed after 48 hours (fig 2B).

DISCUSSION

The results from the present investigation do not support the assumption that postinjection rest retards glucocorticoid resorption after IA administration. This is in accordance with the findings in our previous study on the same patients, which showed no difference in systemic glucocorticoid effects on bone metabolism after IA THA injection between mobile and resting patients.⁹ Consequently, explanations other than decreased steroid resorption should be considered for the noted beneficial effect of rest after IA glucocorticoid treatment for knee synovitis.

We also observed that the THA resorption varied considerably between patients, but no significant difference in serum THA levels could be detected between the two patient groups. To explore fully minor differences in THA resorption, much larger patient cohorts would have been needed, but this was not possible for practical reasons.

Our study also shows that the influence of IA glucocorticoid injections on hormone production of the HPA axis is considerable, but short term and reversible. This finding supports previous studies showing that suppression of the HPA axis after IA administration remains up to 1 week.^{10–11} Despite the fact that the mean serum cortisol levels rapidly normalised, in two of our patients low serum cortisol levels persisted during the observation period. Thus, the duration of the recovery period may vary between individual patients,

and one published case of a patient with adrenal insufficiency after frequent THA injection has been reported.¹²

In conclusion, the interaction between the anti-inflammatory effects of IA glucocorticoids and the beneficial effects of short term joint rest need to be studied further, as well as the side effects on the HPA axis.

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REFERENCES

- 1 **Chakravarty K**, Pharoah PDP, Scott DGI. A randomized controlled study of postinjection rest following intra-articular steroid therapy for knee synovitis. *Br J Rheumatol* 1994;**33**:464–8.
- 2 **Neustadt DH**. Synovitis of the knee. Effects of postinjection rest. *Clin Rheumatol Pract* 1985;**3**:65–8.
- 3 **Arnett FC**, Edworthy SM, Bloch DA, Shane DA, Fries JF, Cooper NS, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;**31**:315–24.
- 4 **Steinbrocker O**, Traeger CH, Betterman RC. Therapeutic criteria in rheumatoid arthritis. *JAMA* 1994;**271**:659–62.
- 5 **Ekdahl C**, Eberhardt K, Andersson SI, Svensson B. Assessing disability in patients with rheumatoid arthritis. *Scand J Rheumatol* 1988;**17**:263–71.
- 6 **Prevoo MLL**, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LBA, van Riel PLCM. Modified disease activity scores that include twenty-eight joint counts. Development of and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;**38**:44–8.
- 7 **Larsen A**, Dale K. Standardized radiological examination of rheumatoid arthritis in therapeutic trials. In: Dumonde DC, Jasani MK, eds. *The recognition of antirheumatic drugs*. Lancaster: MTP Press, 1978:285–92.
- 8 **Weng N**, Halls TDJ. Systematic troubleshooting with LC/MS/MS. *BioPharm* 2001;**14**:28–38.
- 9 **Weitof T**, Larsson A, Saxne T, Rönnblom L. Changes of cartilage and bone markers after intra-articular glucocorticoid treatment with and without postinjection rest in patients with rheumatoid arthritis. *Ann Rheum Dis* 2005;**64**:1750–3.
- 10 **Armstrong RD**, English J, Gibson T, Chakraborty J, Marks V. Serum methylprednisolone levels following intra-articular injection of methylprednisolone acetate. *Ann Rheum Dis* 1981;**40**:571–4.
- 11 **Derendorf H**, Möllmann H, Gruner A, Haack D, Gyselby G. Pharmacokinetics of glucocorticoid suspensions after intra-articular administration. *Clin Pharmacol Ther* 1986;**39**:313–17.
- 12 **O'Sullivan MM**, Rumpf WR, Jones MK, Williams BD. Cushing's syndrome with suppression of the hypothalamic-pituitary-adrenal axis after intra-articular steroid injections. *Ann Rheum Dis* 1985;**44**:561–3.