Comparison of Oral Dexamethasone and Prednisolone in a Mouse Model of Glucocorticoid-Induced Osteoporosis

MI Suominen1, JP Rissanen1, S Ylönen2, H Schäcke1, U Zügell1, JM Halleen1
Pharmatest Services Ltd, Turku, Finland, 2Schering AG, Berlin, Germany.

Introduction
Both prednisolone and dexamethasone have been used to induce osteopenia in mice, but with different study settings. Prednisolone has been used as a slow-releasing pellet with doses under 3 mg/kg/day in male Swiss Webster mice (1) whereas dexamethasone has been used with doses of 1, 5 and 10 mg/kg i.p. in female Balb/c mice (2). Apparently these study settings have many important differences and the doses are surprisingly different considering that dexamethasone is much more potent than prednisolone. Here we wanted to study the bone effects of these two glucocorticoids with a daily oral dosing regimen.

Aim of the study
This study aimed to compare dexamethasone and prednisolone in the same study setting and to establish a dose-response for oral prednisolone. We compared the bone effects of 4-week daily oral dosing of these two glucocorticoids on 12-week old intact Balb/C male mice.

Materials and Methods
Three-month old Balb/C/derived mice were randomly divided into 5 groups (n = 8 in each group) according to body weights as follows: 1) Control group receiving vehicle (Group “Control”); 2) Dexamethasone 10 mg/kg/day (group “D10”), 3) Prednisolone 3 mg/kg/day (group “P3”), 4) Dexamethasone 10 mg/kg/day (group “D10”), 5) Prednisolone 30 mg/kg/day (group “P30”). Treatment was continued daily for 28 days. Fasting blood samples were collected before the beginning of administration and at days 14 and 28. The bone formation marker serum osteocalcin was measured using a commercially available immunoassay (Mouse Osteocalcin IRMA Kit, Immunotopics, Inc., San Clemente, California). Bone mineral density (BMD) measurements were performed by peripheral quantitative computed tomography (pQCT) in vivo from the left tibia before beginning of administration and at the end of the study. Static and dynamic histomorphometric analysis was performed from left proximal tibia and femoral diaphysis at 4 and 28 weeks. Relative changes of pQCT parameters and osteocalcin values were calculated by dividing the value of each individual with its own baseline value. Statistical analysis was performed using one-way ANOVA and Dunnett’s t-test for Post Hoc comparison. The assumptions for normality or homogeneity of variances were not met even after transformations. Kruskal-Wallis test with Mann-Whitney for pairwise comparisons was used. All glucocorticoid groups were compared with the control group and a p-value = 0.05 was considered statistically significant.

Histomorphometry of cortical bone

Histomorphometry of trabecular bone

Summary
In pQCT measurements, significant changes were observed in cortical bone but not in trabecular bone (data not shown).

• The changes in cortical bone resulted in significant decreases of polar moment of inertia and strain strength index.

• Bone formation marker serum osteocalcin was decreased already on day 14.

• Bone formation and mineral apposition in cortical bone decreased dramatically with all doses of glucocorticoids.

• Dexamethasone 10 mg/kg/day had less effect on mineral apposition rate in trabecular bone than 10 and 30 mg/kg/day of prednisolone.

• Significant changes were not found in trabecular bone by static histomorphometry, although 30 mg/kg/day prednisolone showed a trend of decreasing trabecular bone volume and trabecular thickness.

Conclusions
Daily oral doses of 10 mg/kg dexamethasone and 30 mg/kg prednisolone have similar significant osteoporotic effects in this intact mouse model.

References

www.pharmatest.fi