INTRAVESICAL IMMUNE SUPPRESSION BY LIPOSOMAL TACROLIMUS IN CYCLOPHOSPHAMIDE INDUCED OVERACTIVE BLADDER

Hypothesis / aims of study

Potent immunosuppressive effect of FK506 (tacrolimus) has encouraged its topical application for achieving local anti-inflammatory effect. However, its poor aqueous solubility presents challenges in formulating safe, biocompatible instillations for bladder. The present study investigated the feasibility of tacrolimus delivery using liposomes for intravesical immunosuppression.

Study design, materials and methods

Adult female Sprague-Dawley rats (52) divided into 4 experimental groups were injected with CYP (200 mg/kg, ip) except for sham (saline injection, ip). Other three groups received either saline (1 cc, retained for 1 hr), liposome (LP-1 cc) or liposomal encapsulated tacrolimus (LFK- 0.2mg tacrolimus/1 ml LP) by intravesical route. Baseline cystometrogram was performed in all the experimental groups except in sham on day 1 before any treatment and on day 3 prior to bladder harvest for histological staining (N=24). In addition, 4-hr baseline urine on day 1 and day 3 was also collected from all experimental groups for urine PGE2 assay and bladder harvested for PGE2 and IL2 assay on day 3 (N=28).

Results

CYP induced bladder inflammation was associated with increased EP4 staining, and bladder overactivity (intercontraction interval 61.0% decrease). In addition, bladder PGE2 and IL2 level were both elevated 3.5 fold and urine PGE2 was increased by 13.8 fold. Rats pretreated with LFK demonstrated suppression of CYP induced inflammatory reaction as revealed by reduced EP4 staining, bladder overactivity and normalized IL 2 and PGE2 levels in tissue and urine. Intravesical LPs pretreatment had no effects on uninjured rat bladder and did not suppress CYP effects.

Interpretation of results

LFK significantly inhibited CYP induced inflammation through the modulation of IL2, PGE2, and EP4 function. These findings support investigation of local LFK for refractory overactive bladder.

Concluding message

This is the first report of intravesical immune suppression in bladder by delivery of tacrolimus using liposomes.

References


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