Prophylactic and therapeutic effects of three different pharmacological agents in the key-hole limpet hemocyanin (KLH)-induced delayed-type hypersensitivity (DTH) model in mice

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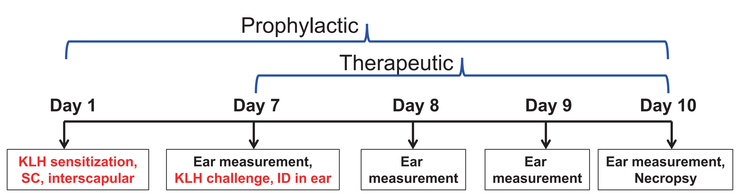
1 Introduction

Delayed-type or type IV hypersensitivity reactions are cell-mediated immune reactions involving activation of T cells and are known to play roles in autoimmune diseases and organ transplantation. In the present study, using two different dosing protocols, effects of clinically used anti-inflammatory, immunosuppressive agents were evaluated in the antigen, KLH-induced DTH model in mice.

2 Methods

Animals were sensitized on Day 1 by subcutaneous (SC) injection with KLH and then challenged with KLH by intra-dermal (ID) injection in the ear to induce the model. Once daily (QD) oral gavage dosing (PO) with budesonide (0.01, 0.1 and 1 mg/kg), cyclosporine A (0.6, 6 and 60 mg/kg) and dexamethasone (0.03, 0.3 and 3 mg/kg) were done from Day 1-10 for the prophylactic effects and Day 7-10 for therapeutic effects. Ear thicknesses were measured on Day 7 before challenge and on Days 8, 9 and 10 at approximately 24h, 48h and 72h post challenge. Animals were sacrificed on Day 10 following the final ear thickness measurements. For measuring overall effects of the test agents, data were converted into area under the curve (AUC) for the ear thickness from Day 7 to Day 10. Data were analyzed using one-way ANOVA and Holm-Sidak's test for multiple comparisons. *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001



3 Results: Effect of Budesonide

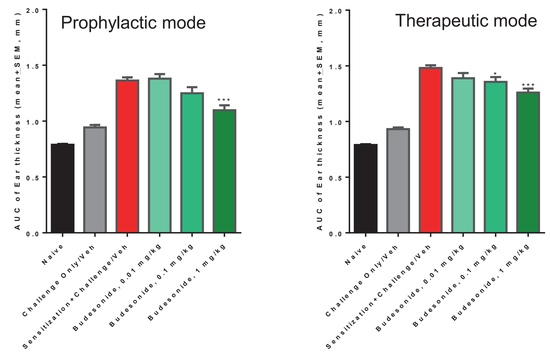


Figure 1: Budesonide at 1.0 mg/kg significantly attenuated ear swelling both in prophylactic and therapeutic dosing mode although some effects were also observed at 0.1 mg/kg in the therapeutic mode. Effects in prophylactic mode was slightly better compared with therapeutic mode.

Effect of Cyclosporine A

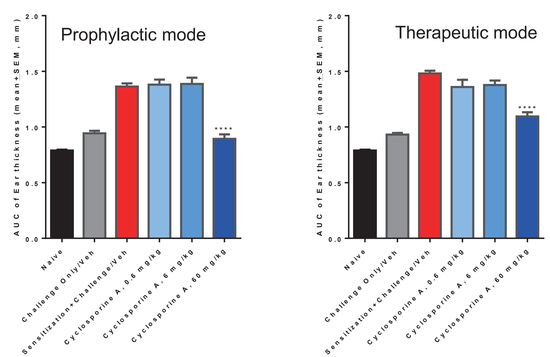


Figure 2: Cyclosporine A significantly attenuated KLH-induced ear swelling at the highest dose level i.e. at 60 mg/kg. Effects in prophylactic mode was better than the therapeutic mode.

Effect of Dexamethasone

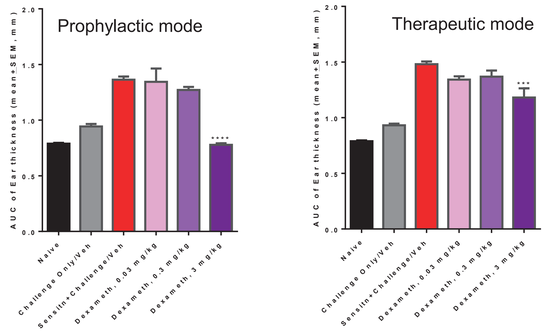


Figure 3: Dexamethasone significantly attenuated KLH-induced ear swelling at the highest dose level (3 mg/kg). Effects in prophylactic mode was better than the therapeutic mode.

Time-course of the effects

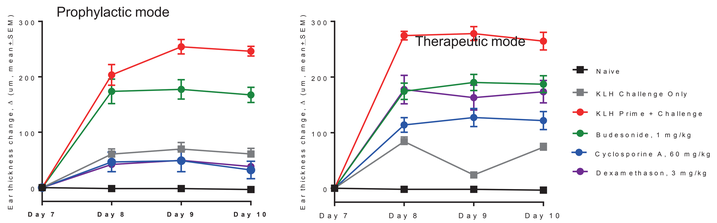


Figure 4: Time course for the effects of top dose levels of the three test agents in prophylactic and therapeutic mode. Cyclosporine A and Dexamethasone had better effects in prophylactic mode.

4 Conclusion

- ❑ KLH induced DTH effects in mice with presence of significant ear swelling at 24h, 48h and 72h post challenge.
- ❑ All three test agents inhibited DTH effects both in prophylactic and therapeutic dosing protocol. Overall, better efficacies were observed in prophylactic dosing mode.