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# Pharmacological characterization of the neonatally sensitized rabbit model and effects of a novel phosphodiesterase (PDE) 4 inhibitor

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The recognition of asthma as an inflammatory disease has led to the search for novel anti-inflammatory agents, the ideal agent being one that exhibited the efficacy of the steroids but without their adverse effects. The neonatally sensitised rabbit model exhibits three characteristic features of asthma: allergen-induced acute bronchoconstriction (ABC), airway hyperresponsiveness (AHR) and eosinophilia (EOS) (Herd & Page, 1996).

Elevation of cyclic-AMP has long been known to suppress cellular activation and theophylline, a non-selective inhibitor of phosphodiesterases (PDE) has been a mainstay treatment in asthma despite its adverse effect profile (Finnerty & Holgate, 1989). PDE4 is the principal cyclic-AMP hydrolysing PDE in many cell types involved in asthmatic inflammation and thus inhibition of PDE4 should be beneficial (Hughes et al, 1997).

We have compared the activity of a novel PDE4 inhibitor (CT2820) against the effects of clinically used agents in the rabbit model of asthma.

Rabbits were sensitised with allergen (*Alternaria tenuis*) within 24h of birth and until 3 months of age (Gozzard et al, 1996). Airway responsiveness to histamine and bronchoalveolar lavage (BAL) were performed 24h before and after allergen challenge. Groups of rabbits (n=6-8) were treated with the steroid budesonide (50μg by inhalation), the $\beta_2$ agonist salbutamol (1mg/kg i.p.), the $LTD_4$ antagonist MK-571 (10mg/kg, i.p.) or theophylline (3mg/kg, i.p.) prior to allergen challenge. CT2820 was administered at 0.3, 1 or 5mg/kg i.p. b.i.d. for two days and a final dose 1h prior to allergen challenge. The effects of these treatments on ABC, AHR and EOS infiltration were evaluated.

Exposure of vehicle treated rabbits to allergen resulted in a immediate 40% increase in airway resistance and fall in dynamic compliance (ABC), followed by a 2-3 fold increase in bronchial reactivity to aerosolized histamine (AHR) and a pronounced EOS 24h later.

Budesonide inhibited the dynamic compliance, but not the resistance component of the ABC. Budesonide also attenuated AHR and EOS. Salbutamol significantly inhibited the ABC but did not effect AHR or EOS. MK-571 inhibited the ABC and AHR but was without effect on the EOS. In contrast, theophylline significantly inhibited the EOS but did not affect ABC or AHR.

CT2820 elicited a dose-related inhibition of all three parameters, the 1mg/kg dose attaining significance ($p<0.05$). None of the compounds, with the exception of salbutamol, caused bronchodilation of basal airway tone.

Another $LTD_4$ antagonist (MK-476) has been shown to exert anti-inflammatory effects in chronic asthma (Leff et al, 1997 a & b), but failed to inhibit allergen-induced changes in sputum EOS, despite beneficial effects on lung function (Grootendoorst et al, 1997), a profile similar to that observed with MK-571 in the rabbit.

Theophylline reduced EOS with no effects on ABC or AHR, consistant with studies in man using chronic low dose theophylline which show significant inhibition of allergen-induced eosinophil recruitment (Sullivan et al, 1994). These data suggest that the rabbit model of asthma is sensitive to clinically used agents and that inhibition of PDE4 results in significant anti-inflammatory effects similar to those observed with budesonide.

The activity of CT2820 is similiar to that of CDP840 in the rabbit model (Gozzard et al, 1996) which exhibited anti-inflammatory activity in an allergen challenge study in man (Harbinson et al, 1997).

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