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CROMOGLYCATE ABSORPTION FROM RABBIT LUNG AFTER ADMINISTRATION OF A DEXTRAN CONJUGATE

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Sodium cromoglycate (cromolyn sodium; SCG) is widely used in the prophylactic treatment of bronchial asthma. Following inhalation, SCG is efficiently absorbed from the lung and its relatively short residence time necessitates frequent dosing, up to eight times daily. This limits the usefulness of the drug. Dextran-drug conjugates have previously been utilized in an effort to prolong the duration and potentiate the action of certain systemically acting compounds including mitomycin C, procainamide and daunorubicin. A dextran ester containing 40% w/w cromoglycate (CG-Dx) was synthesized. The effect of this conjugation upon cromoglycate (CG) pharmacokinetics after pulmonary administration was investigated.

A group of four male New Zealand White rabbits were given solutions of; SCG intravenously (i.v.), 1 mg/kg and intratracheally (i.t.), 4 mg/kg; CG-Dx i.t., 10 mg/kg; FITC-dextran (FITC-Dx) i.t., 5 mg/kg, in a randomised cross-over designed study. Plasma concentrations of CG were determined by an HPLC assay method. Ultrafiltered plasma samples were injected onto an HPLC column (Spherisorb S5-ODS2) which was eluted with 0.067 M phosphate buffer, pH 7.4, containing 0.064% tetrabutyl ammonium hydroxide and 36% methanol. The column effluent was monitored at 238 nm and peak areas quantified using a computing integrator.

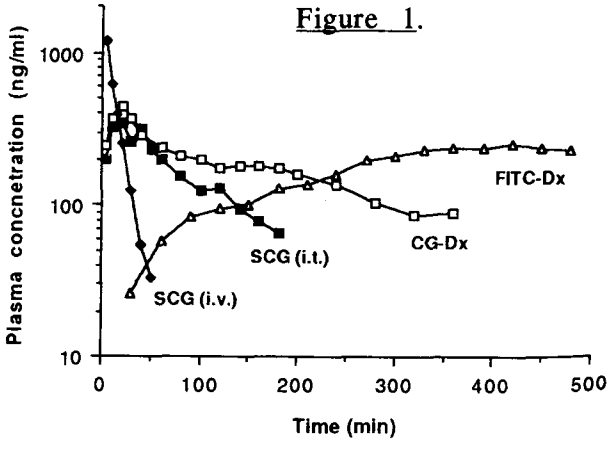
Mean plasma concentration-time profiles of CG following i.v. and i.t. administration of SCG and i.t administration of the CG-Dx and plasma fluorescence after i.t. FITC-Dx conjugate are shown in Figure 1. After i.v. administration of SCG, CG was rapidly eliminated from plasma with a half-life of 7 minutes (Table 1). Following i.t. administration of SCG, plasma concentrations of CG peaked fairly rapidly and then declined with a half-life which was significantly longer than was seen after i.v. dosing. The post-peak half-life seen after i.t. administration of SCG is thus a reflection of its absorption from the lung. After i.t. administration of the CG-Dx conjugate, plasma concentrations of CG increased rapidly subsequently reaching a plateau. The time to reach peak concentration (t_{max}) showed considerable variation but was not significantly different from that observed after i.t. administration of SCG. The mean post-plateau half-life was significantly longer than was seen after i.t. SCG administration and indicates a much longer persistence of the conjugate within the lung. There were no significant differences in the dose normalized AUCs of i.t. SCG and CG-Dx.

Table 1. Cromoglycate pharmacokinetic parameters (mean ± s.e.m.)

	SCG (i.t.)	CG-Dx (i.t.)
$t_{1/2}$ (min)	73 ± 12*	176 ± 30*
t_{max}(min)	23 ± 6	64 ± 46
C_{max}(ng/ml)[a]	402 ± 140	195 ± 29
AUC (ng h/ml)[a]	545 ± 180	526 ± 56
F(%)	41 ± 13	40 ± 6

[a]Normalized for a 4 mg/kg dose.
*Significantly different ($p<0.05$) from other treatments (2-way ANOVA and Duncan's multiple range test).

Figure 1.



The absorption of i.t. FITC-Dx was markedly slower than that of i.t. CG-Dx (Fig. 1). Lung absorption rate constants decrease with increasing molecular weight of both hydrophilic solutes (Schanker et al, 1986) and FITC-dextrans (Takada et al, 1978). Since CG-Dx and FITC-Dx were of similar molecular weight, the more rapid appearance of CG in plasma indicates that CG-Dx is hydrolysed in the lung before absorption.

Schanker, L.S., et al (1986) Drug Metab. Dispos. 14: 79 - 88
Takada, K., et al (1978) J. Pharm. Dyn. 1: 281-287