Preliminary studies on SL 75212, a new potent cardioselective β-adrenoceptor antagonist

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SL 75212, (±)-1-(isopropylamino)-3-(p-(cyclopropylmethoxyethyl)-phenoxy)-2-propranol.HCl, is a new potent cardioselective β-adrenoceptor antagonist devoid of intrinsic sympathomimetic activity with very weak local anaesthetic properties.

In isolated rat atria, the inhibition of isoprenaline induced chronotropic (spontaneously beating right atria) and inotropic (left atria paced at 1 Hz) effects by SL 75212 was comparable to that observed with (±)-propranolol and several times more potent than either metoprolol, atenolol or practolol (Table 1). SL 75212, atenolol, practolol and metoprolol, in contrast to (±)-propranolol, were weak antagonists of the isoprenaline induced relaxation in isolated guinea pig tracheal chains contracted with carbachol (Table 1). The ratio between the pA_2 values for SL 75212, atenolol, practolol, metoprolol and (±)-propranolol against the effects of isoprenaline in isolated rat right atria and guinea pig tracheal chains were 224, 56, 45, 32 and 1, respectively. Therefore, *in vitro* SL 75212 appears to possess the highest cardioselective properties of the compounds tested.

In intact anaesthetized rats and dogs, SL 75212 and (±)-propranolol (0.01–1.0 mg/kg, i.v.) similarly inhibited in a dose-related manner the tachycardia to isoprenaline (0.3 μg/kg, i.v.). These antagonists were more potent (2–4 times) than metoprolol. However, metoprolol and SL 75212 only slightly antagonized the hypotensive action of isoprenaline. In contrast, (±)-propranolol was slightly more active in inhibiting the isoprenaline induced hypotension than the tachycardia response. When SL 75212 was given orally to rats or dogs, its β-adrenoreceptor blocking activity was more pronounced (at least 10 times) and of a longer duration than those of (±)-propranolol and metoprolol.

In reserpinised (5 mg/kg, s.c. 24 h before the experiment), bivagotomized rats SL 75212 (0.01–1.0 mg/kg, i.v.) did not produce positive chronotropic effects which was in contrast to oxprenolol, pindolol and practolol. Hence, SL 75212 is devoid of intrinsic sympathomimetic activity.

In the frog sciatic nerve preparation the calculated concentration of (±)-propranolol needed to decrease the height of evoked action potentials by 50% (EC_{50}) was approximately 14 mM. The EC_{50} of SL 75212 was greater than 300 mM indicating that SL 75212 possesses relatively weak local anaesthetic properties compared to (±)-propranolol.

Table 1

	Rat Atria				*Guinea-pig Tracheal chain*		
	Inotropism		*Chronotropism (C)*		*Relaxation (R)*		*Ratio*
Antagonist	(pA_2)	(*P.R.*)	(pA_2)	(*P.R.*)	(pA_2)	(*P.R.*)	(*C/R*)
SL 75212	8·29	1.74	8.53	1.48	6.18	0.02	224
Atenolol	7.68*	0.43	7.55*	0.15	5.80*	0.01	56
Practolol	7.30*	0.18	6.73*	0.02	5.08*	0.001	45
Metoprolol	7.45*	0.25	7.64*	0.19	6.14	0.02	32
(±)-Propranolol	8.05	1.00	8.36	1.00	7.90*	1.00	3

* pA_2 value significantly different from SL 75212 (Student's t-test, $P < 0.05$).
All pA_2 values are the means of 4–6 experiments.
The potency ratios [P.R. = antilog (pA_2 antagonist—pA_2 propranolol)] are calculated with respect to (±)-propranolol.