Pharmacological studies with LL 21-945, a new beta-adrenoceptor blocking agent with a long duration of action

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A series of compounds were synthesized with the intention of producing a substance which would provide sustained β-adrenoceptor blockade over a period of 24 hours. It was considered possible that an ester group at the β-carbon atom of the side chain which would be only slowly hydrolysed could result in a prolonged action.

Bulky acyl radicals were found the most effective in retarding hydrolysis of the ester group. Of the substances prepared, LL 21-945 (4-[3-tert-butylamino-2-pivaloyloxypropoxy]-9-fluorenon-hydrogenmalonate) was selected for further pharmacological study.

In isolated atria, LL 21-945 was similar in potency to propranolol in inhibiting positive chronotropic responses to isoprenaline. The pA_2 was 8.6 for LL 21-945, 8.4 for propranolol and 9.6 for pindolol.

LL 21-945 depressed contractile force in spontaneously-beating atria and caused a reduction in excitability and prolongation of the relative refractory period in electrically-stimulated atria. Quantitatively similar effects were obtained with propranolol and pindolol at concentrations 0.3 and 4.4 times that required for LL 21-945, respectively. In anaesthetized cats depleted of catecholamines, LL 21-945 induced increases in heart rate from 20 μg/kg i.v. It was less active in this respect than pindolol; propranolol displayed no beta-adrenoceptor stimulant activity at doses up to 2.5 mg/kg i.v.

In anaesthetized dogs, LL 21-945 was 1.2 (fiducial limits 1.0-1.6) times as active as propranolol in inhibiting the positive chronotropic effects of isoprenaline (0.5 μg/kg i.v. 6 point assay, $n = 5$); pindolol was 14.2 (fiducial limits 10.6-19.0) times as active as propranolol. Maximum inhibitory effects were usually observed 2.5 h after administration of LL 21-945. No diminution of the effects occurred during the subsequent 2.5 hours. In contrast, maximum effects occurred within 5 min of administration of propranolol and pindolol; with both drugs, beta-adrenoceptor blockade diminished during the 5 h experimental period (Saameli, 1972). Propranolol (256 μg/kg i.v.) and pindolol (16 μg/kg i.v.) inhibited isoprenaline responses by 77 ± 3% and 85 ± 2% (± s.e. mean, $n = 5$), respectively. Only 20 ± 7% inhibition remained 2.5 h after administration of propranolol, whereas with pindolol, isoprenaline responses were still inhibited by 60 ± 6% after 5 hours.

The duration of action of LL 21-945 was investigated in two conscious dogs and compared with that of pindolol. Heart rate increases following isoprenaline (0.25-0.4 μg/kg i.v.) were inhibited by 87-100% 2 h after administration of LL 21-945 (150 μg/kg i.v.). After 39 h, responses were still inhibited by 30-50%. Pindolol (16 μg/kg i.v.) inhibited isoprenaline responses by 80-100% within 5 min of administration. After 9 h, responses were inhibited by 22-27%; recovery was complete after 24 hours.

In view of the long duration of action of LL 21-945, the possibility was considered that a cumulative effect might occur on repeated administration. Four doses of 150 μg/kg i.v. were given to two dogs at 24 h intervals. Dose-response curves for isoprenaline (positive chronotropic effects) were determined immediately before each dose and 24 h after the last dose. The dose-response curve obtained 24 h after the first dose was displaced to the right. Curves obtained 24 h after each of the subsequent doses showed no further shift.

Reference

SAAMELI, K. (1972). Die pharmakologische Charakterisierung β-sympathicolytischer Substanzen, pp. 3-30. In: *Die therapeutische Anwendung β-sympatholytischer Stoffe.* ed. Dengler, H.J., Stuttgart–New York: F.K. Schattauer Verlag.