Comparison of New β-Adrenergic Blockers, C-3, Kö1366, Y-6124 and YB-2, with Pindolol and Propranolol in the Blood Perfused Canine Papillary Muscle Preparation

In a previous study[1], we assessed the β-adrenergic blocking activity of 7 well-known compounds against the positive inotropic effect of norepinephrine in the blood-perfused canine papillary muscle. Results were as follows: pindolol (LB 46) > practolol (ICI 50172) = alprenolol (H 56/28) = propranolol > sotalol (MJ 1999) > DCI > methxamine (10:1:1/3:1/10: less than 1/10). In this paper the β-adrenergic blocking activity of newly synthesized compounds, Kö1366, C-3, Y-6124 and YB-2, were compared with that of propranolol and pindolol in the same preparation.

The heart was removed from a dog anesthetized with ether and plunged into the cold Tyrode's solution. The anterior septal artery was dissected and cannulated. All branches except the arteries to the anterior papillary muscle were ligated and unirrigated part of muscle was removed. The isolated muscle was perfused with the arterial blood conducted from the carotid artery of a heparinized donor dog by the aid of a Sigma-motor pump. A pneumatic resistance was placed in parallel with the perfusion system so that a constant perfusion pressure at 100 mm Hg was maintained. The papillary muscle preparation was placed in a glass container which was warmed at 38–39°C by circulating warm water. The tendinous end of the papillary muscle was connected to a force displacement transducer (Grass FT 03 B) by a fine silk thread and stretched with a weight of 1 g. The papillary muscle was driven electrically at a frequency of 120/min with rectangular pulses of 0.6–1 V and 5 msec duration. A very stable contractile force was developed over 10 h, and then several compounds could be compared in one papillary muscle preparation. The details of the experimental set-up were described in the previous paper[2]. Drugs used were as follows: L-norepinephrine, DL-propranolol hydrochloride, DL-pindolol, DL-5-methyl-8-(2-hydroxy-3-*tert*-butylamino-propoxy) coumarin hydrochloride[3] (C-3, Sankyo), DL-*o*-2-hydroxy-3-(*tert*-butylamino)-propoxy-benzonitrile hydrochloride[4] (Kö166, Boehringer Ingelheim), DL-1-*tert*-butylamino-3-[*o*-(tetrahydro-furfuryloxy)phenoxy]-2-propanol hydrochloride[5] (Y-6124, Yoshitomi Seiyaku) and DL-1-(7-indenyloxy)-3-isopropylaminopropane-2-ol hydrochloride[6] (YB-2, Yamanouchi Seiyaku). All of the agents were injected intra-arterially with microsyringes in a volume of 10–30 µl for 4 sec.

Norepinephrine was used in a dose of 0.3 nmol as an agonist. Successive administrations of this dose of norepinephrine caused almost the same response in every trial. Typical results are shown in Figure 1 (Experiment No. 9). Different doses of an antagonist were given and 0.3 nmol of norepinephrine was challenged 1 and 10 min after the administration of an antagonist, and then at 10 min intervals until the control response was obtained. Thus the intrinsic activity of β-adrenergic agents and their blocking activity on the positive inotropic response to norepinephrine could be investigated. Kö1366 frequently and pindolol occasionally produced the positive inotropic response in doses which blocked the positive inotropic response to norepinephrine. The other agents, C-3, Y-6124, YB-2 and propranolol, with a dose as large as 30 nmol (C-3, 10 nmol) occasionally caused a slight negative inotropic response.

Dose-effect curves for 4 new and 2 authentic β-adrenergic blocking agents are shown in Figure 2. These values were calculated from the data obtained 1 min after the administration of antagonists. Kö1366 was the most active, pindolol and C-3 came next, and Y-6124 and YB-2 had almost the same potency as propranolol. Relative potencies are as follows: Kö1366 > pindolol > C-3 > Y-

[1] K. Hashimoto, M. Endoh, K. Tamura and N. Taira, Experientia *26*, 757 (1970).
[2] M. Endoh and K. Hashimoto, Jap. J. Physiol. *20*, 320 (1970).
[3] Y. Sato, Y. Kobayashi, T. Nagasaki, H. Takagi, T. Oshima, S. Kumakura, K. Nakayama and H. Koike, Chem. pharm. Bull. Tokyo, in press.
[4] A. Engelhardt and W. Traunecker, Naunyn-Schmiedebergs Arch. Pharm. Berl. *263*, 203 (1969).
[5] M. Nakanishi, H. Imamura, T. Nakamura and T. Kimura, J. pharm. Soc. Japan *91*, 1037 (1971).
[6] S. Tachikawa, M. Takeda and T. Takenaka, Folia pharmac. jap., in press.

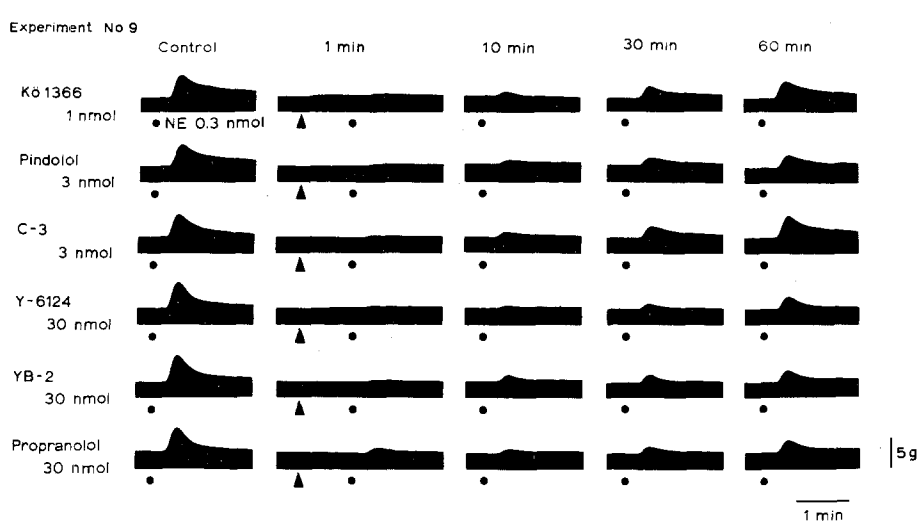

Fig. 1. Comparison of 6 β-adrenergic blocking agents in the blood-perfused papillary muscle preparation. Triangles indicate the time when test agents (antagonists) were administered and dots indicate that for the injection of norepinephrine (agonist). Experiment was done in the same preparation (Experiment No. 9).

6124 = YB-2 = propranolol which roughly corresponds to 30, 10, 5 and 1. The duration of blocking activity was comparatively shorter in Kö1366 and C-3 than in other 4 agents as indicated in Figure 1.

The present result of β-adrenergic blocking activity on the inotropic response is almost the same to that on the chronotropic response of the excised and blood-perfused sino atrial node preparation of dog. We conclude that there may be probably no difference in the β-blocking activity of 6 compounds between on the chronotropic and inotropic responses in dog.

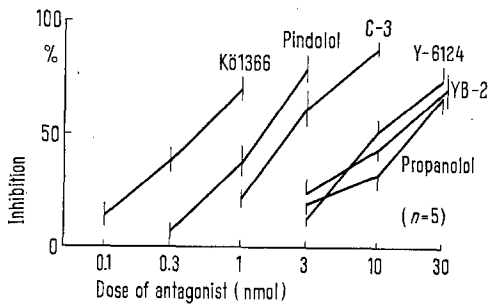

Fig. 2. Dose-effect curves for 6 β-adrenergic blocking agents on the positive inotropic response caused by 0.3 nmol of norepinephrine. Oridinates: Percent inhibition of the positive inotropic response to norepinephrine. Abscissas: Dose of antagonists. Each points indicate the means and vertical bars refer to S.E.

Zusammenfassung. Es wurde die Potenz sechs β-adrenergischer Blockierungsmittel auf positiv inotrope Wirkung von Noradrenalin am isolierten, Blut zuführenden Papillarmuskel des Hundes vergleichend untersucht. Die Reihenfolge der Wirksamkeit: Köl366 > pindolol > C-3 > Y-6124 = YB-2 = propranolol (30:10:5:1).

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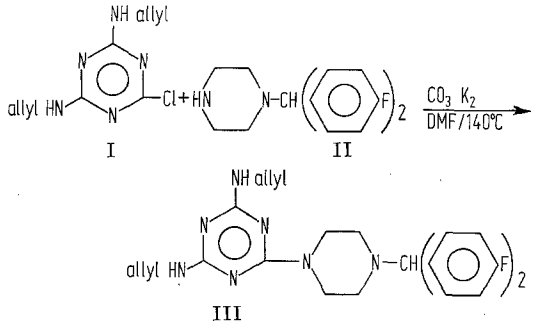
A Long Acting Respiratory Stimulating Agent: 1-(4,6 *Bis* allylamino-2-s-triazinyl)-4-(*Bis p*-fluorobenzhydryl) Piperazine (S 2620)

Todays respiratory stimulants for treatment of respiratory insufficiency are potent CNS stimulating substances; they induce convulsions even in the presence of CNS depressants such as barbiturates. Besides, they increase oxygen consumption and CO_2 production, so that the resulting hyperventilation does not parallel the concomitant arterial Pa CO_2 lowering. We searched for compounds which act on the respiratory tract by the intermediary of both carotid and aortic chemoreceptors and without CNS stimulating activity and selected among 50 piperazine derivatives[1] the title compound (S 2620) III which was synthesized according to the following scheme:



2-Chloro-4,6-bis allylamino-s-triazine I was prepared according to reference[2]. 1-(*Bis p*-fluorobenzhydryl) piperazine II was prepared through condensation of *bis-p* fluorobenzhydryl chloride and anhydrous piperazine. 1-(4,6-*Bis* allylamino-2-s-triazinyl)-4-(*bis p*-fluorobenzhydryl) piperazine III has mp 181 °C. The *bis* (methane sulfonate) of III has mp 243 °C (dec); UV $\lambda_{max.}^{EtOH}$ nm (log ε); 227 (4,52), 246 (4,53), 271_{Sh} (3,28).

In anaesthetized and unanaesthetized dogs, S 2620, administered by the i.v. (0.2 to 3 mg/kg) or oral route (2 to 5 mg/kg), induced a long lasting increase of ventilation without changes of oxygen consumption, carbon dioxide production and respiratory quotient. The arterial Pa CO_2 decreases with the increase of blood pH. Neither intracisternal nor intravertebral injection of S 2620 had any significant effect on respiration. The respiratory stimulation is abolished by vagotomy and carotid bodies denervation. In consequence, S 2620 is a long lasting chemoreflex stimulant without complication of cortical excitation.

The stimulating effect of S 2620 upon respiration is not influenced during oxygen administration, metabolic acidosis and alkalosis, after i.v. injection of mecamylamine, hexametonium, atropine, eserine and reserpine. The LD_{50} (mice) of III (*bis* methane sulfonate) were found 210 mg/kg (i.v.), 390 mg/kg (i.p.) and > 2 g/kg (p.o.).

In clinical studies, the effect of acute and chronic administration of S 2620 used for treatment of acute respiratory insufficiency has been observed in patients with chronic pulmonary emphysema and hypercapnia as in barbiturate intoxication. In every case, S2620 leads to hyperventilation with a long lasting lowering of arterial Pa CO_2 as well as to an increase in arterial oxygenation. Full reports of the chemistry and pharmacology[3] of this new agent will be presented in the near future.

Résumé. La (*Bis* allylamino-4,6 s-triazinyl-2)-I (*bis p*-fluorobenzhydryl)-4 pipérazine est un stimulant respiratoire à longue durée d'action et dépourvu d'action stimulante du système nerveux central.

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[1] Manuscript in preparation.
[2] R.D. DUNLOP and J. H. GARDNER, J. Am. chem. Soc. *55*, 1665 (1933).
[3] M. LAUBIE and F. DIOT, J. Pharmac., in preparation.