

A new peripheral and coronary vasodilator substance of the β -aminoketone group

SIR,—The pharmacological effects of β -aminoketones are many. Thus, their action on the central nervous system (Brit. Pat. 1961), their analgesic (Ruschig, Schmitt & Meixner, 1962), adrenergic neuron blocking (de Stevens, 1961), antinicotinic (Nádor & Porszász, 1958), antibacterial (Magarian & Nobles, 1967) properties have been investigated. In the course of clinical trials of an antinicotinic action of 2-methyl-1-piperidino-3-(*p*-tolyl)-propan-3-one hydrochloride (Mydocalm), a vasodilator effect was observed (Molnár, 1961). This was substantiated by animal experiments (Solti, Iskun & others, 1964). This effect of the aminoketone has been investigated in a series of new compounds and 3-(*p*-octylphenyl)-1-piperidinopropan-3-one hydrochloride (N-1113) proved to be a significant peripheral and coronary vasodilator.

Table 1 illustrates the increase of blood flow following different doses of papaverine and N-1113 in the femoral artery of cats weighing 3 to 3.5 kg anaesthetized with pentobarbitone (40 mg/kg i.p.). Measurements were made with a Nycotron electromagnetic blood flow meter. The substances were administered in a 0.2 ml volume intra-arterially distally from the flow probe

TABLE 1. VASODILATOR EFFECT ON THE FEMORAL ARTERY OF THE ANAESTHETIZED CAT

Drug	Dose mg i.a.	n	Flow increase	
			Mean \pm s.e. (ml)	%*
Papaverine	0.09	4	2.9 \pm 0.3	40
	0.27	9	4.8 \pm 1.4	44
	0.37	3	7.0 \pm 2.2	96
	0.50	3	8.2 \pm 2.6	112
	0.81	12	9.0 \pm 1.5	124
	1.12	4	12.5 \pm 2.9	170
	2.43	6	12.6 \pm 1.6	173
N-1113	0.03	3	3.5 \pm 0.3	48
	0.06	4	4.1 \pm 0.3	56
	0.09	7	5.5 \pm 1.3	75
	0.12	6	7.9 \pm 1.1	95
	0.27	14	10.4 \pm 1.8	142
	0.81	8	14.5 \pm 3.0	198

* Value related to the basic flow during the period of the effect.

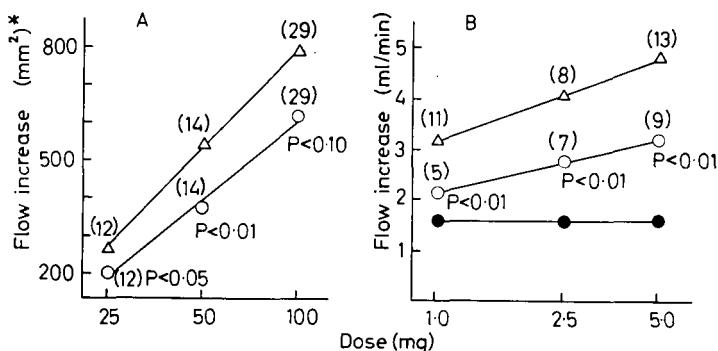


FIG. 1. Coronary flow increase on isolated heart (A) and anaesthetized animal (B) on the effect of Prenylamine (\circ — \circ) and N-1113 (Δ — Δ). \bullet — \bullet , Basic flow. Figures in parenthesis indicate the number of experiments on which the mean was based. P = statistical significance of identical doses.

* Increase of perfusion was evaluated planimetrically.

in a fine polyethylene cannula inserted into a side branch of the artery. In this manner femoral arterial flow was not interrupted. The increased flow following the effect of the drug is obtained by subtracting from the total flow from the beginning of the effect, the basic flow for the same period.

The dose response curves derived from the results in Table 1 are parallel, thus a similar mode of action may be assumed and in a weight basis N-1113 has some three times the potency of papaverine. Increase of flow by both substances at these doses subsides within 1 to 3 min.

Coronary flow was measured on the cat isolated heart (Langendorff) and also by measuring with a drop counter the quantity of blood flowing from the cannula inserted in the coronary sinus of an anaesthetized cat with open thorax. In the heart preparation the drugs were administered in the perfusion fluid in a volume of 1 ml, in the anaesthetized animal, into the femoral vein.

Fig. 1 shows that the effect of N-1113 exerted on the amount of blood flowing through the coronary artery in *in vivo* and *in vitro* experiments is significantly greater than that caused by prenylamine in the same dose. The duration of action of N-1113 is 6 to 7 min, which is about 2.5 to 3 times that of prenylamine.

Pharmacological Laboratory,
Chemical Works of Gedeon Richter Ltd.,
Budapest, Hungary.

E. KÁRPÁTI
L. SZPORNÝ
L. DÖMÖK

Institut of Experimental Medical Research,
Hungarian Academy of Sciences,
Budapest, Hungary.

K. NÁDOR

July 26, 1968

References

- Brit. Pat. (1961) Upjohn 885,608.
de Stevens, G. (1961). U.S. Patent 3,000,946.
Magarian, R. A. & Nobles, W. L. (1967). *J. pharm. Sci.*, **56**, 987-992.
Molnár, L. (1961). *Gyógyszereink*, **11**, 11-16.
Nádor, K. & Porszász, J. (1958). *Arzneimittel-Forsch.*, **6**, 313-319.
Ruschig, H., Schmitt, K. & Meixner, W. (1962). DAS, 1.124.952.
Solti, F., Iskum, M., Rév, J. & Nagy, J. (1964). *Belorvosi Arch.*, **17**, 312-315.