

THE INFLUENCE OF SOME NEW NOR-CAMPHANE DERIVATIVES ON THE CORONARY FLOW

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A new compound 2-Ethylamino-3 phenyl nor-camphane hydrochloride was synthesized by E-Merck and given the code name of H-610. The compound stimulates motor activities, possesses marked antifatigue properties and also produces an increase in the coronary flow in the isolated rabbit hearts (3,4). The stimulant action on the central nervous system reduces the potential value of the compound as a coronary vasodilator. Searches were, therefore, made amongst chemical analogues for compounds with coronary vasodilator activity but without stimulant action on the nervous system. Four such compounds were studied and the results are now being reported.

MATERIALS AND METHODS

In-vitro studies—The effect of continuous perfusion of drugs in varying concentrations were studied on the isolated heart of the rabbit and the guinea-pig by the method of Langendorff(1). Five to six experiments were performed with each concentration of the drugs under test. Initially the coronaries were perfused with Ringer-Locke solution in order to determine the basal flow per minute. When a steady state has been reached the perfusion was switched over to Ringer-Locke solution containing the test drug.

In-vivo studies—Dogs of either sex weighing between (8-14 kg) were anaesthetised with pentobarbitone (30 mg/kg) intravenously. The heart was exposed under positive pressure artificial respiration. The left anterior descending branch of the coronary artery was cannulated for estimation of blood flow from the branch. The blood flow was recorded per minute and the collected blood reinfused through the femoral vein. Coagulation was prevented by intravenous injection of heparin (500-1000 u/kg).

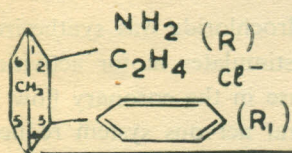
In control studies, it was seen that the flow from the artery remains constant in presence of uniform systemic blood pressure. A reduction in flow may be due to either coronary Vasoconstriction or fall in systemic blood pressure. Sodium nitrite produced an increase in coronary flow inspite of lowering of systemic blood pressure. This method was standardised in the laboratory, before the experiments were performed.

The effect of test drugs on systemic arterial pressure was studied according to standard method (1). The action on peripheral blood vessels of rat hind limbs was studied according to the method of Sanyal and West (2).

Drugs—The compound norcamphane hydrochloride (H-610), has a chemical formula of 2-ethylamino-3 phenyl bicyclo (2,2,1) heptane hydrochloride. In all other related compounds, a phenyl group is attached to the carbon in position 2 along with various substitutions in position 3 (Table I). All compounds were soluble in water and were used in varying concentrations ranging from 10^{-3} g/ml to 10^{-8} g/ml. A concentration of 10^{-6} g/ml was used in comparison studies. Sodium nitrite in the same concentration was used for purposes of comparison.

TABLE I

STRUCTURAL FORMULA OF H 610 AND ITS VARIOUS ANALOGUES

2 ETHYLAMINO 3-PHENYL BICYCLO (2,2,1)
HEPTANE HYDROCHLORIDE (H 610)

Sr. NO	CODE NO.	SUBSTITUENTS	
		R	R ₁
1	H 475	C ₆ H ₅	-NH ₂
2	H 810	C ₆ H ₅	-N $\begin{cases} \text{C}_2\text{H}_5 \\ \text{CH}_2 \cdot \text{CH}_2 \cdot \text{OH} \end{cases}$
3	H 1000	C ₆ H ₅	-N $\begin{cases} \text{CH}_2\text{CH}_3 \\ \text{CH}_2 \cdot \text{CH} : \text{CH}_2 \end{cases}$
4	H 799	C ₆ H ₅	-CH ₂ -NH ₂

RESULTS

Studies on Isolated Rabbit Heart

The compound H-610 was given as continuous perfusion in varying concentrations as mentioned above. There was a reduction in the force of myocardial contraction and an increase in the coronary flow, but the heart rate was not affected. The percent increase in coronary flow has been plotted against concentration in log scale in Fig. 1. The increase in the coronary flow occurred within one minute and returned to basal values within one hour despite the presence of the drug in the perfusion fluid.

The other compounds produced similar effects but were different in potency and the duration of action were also different. The time course of action of all drugs including the reference drug sodium nitrite have been shown in figure 2, and a comparison of the maximum effects have been depicted in figure 3. The actions of the substitute compounds were of short

NORCAMPHANE DERIVATIVE & CORONARY FLOW

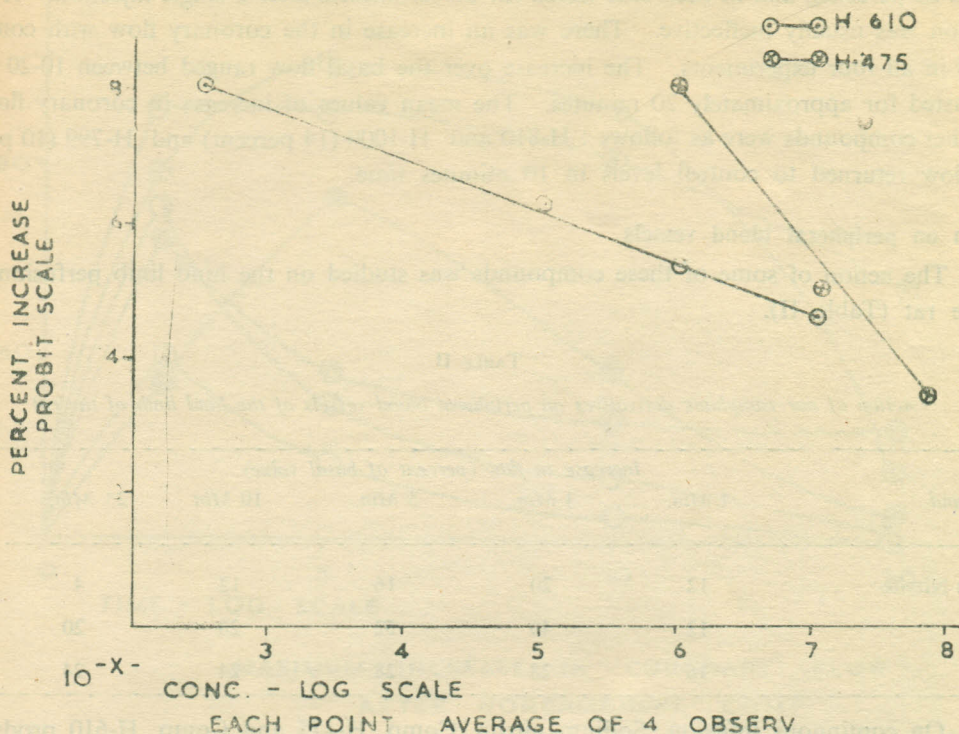


Fig. 1

duration. The compound H-475, which had the smallest side chain in R_1 position was seen to be the most potent compound.

There was an immediate increase in coronary flow with sodium nitrite. The maximum increase occurred within one minute, and the total duration of action was 30 minutes (3 experiments).

All the compounds with the exception of H-810 produced myocardial depression (Fig.4). There was 25% reduction in myocardial excursions with sodium nitrite. A myocardial depression may lead to an increase in coronary flow due to mechanical factors. As such coronary flow studies were also undertaken after induction of ventricular fibrillation. The compounds produced comparable increases in coronary flow in such a set up as well. The compound H-810 in a concentration of 10^{-6} g/ml produced a transient myocardial stimulation.

Similar results were obtained in perfusion experiments with the isolated guinea-pig heart.

In vivo Studies in the Dog

Five experiments were performed with the compound H-610 (10 mg/kg) and in all experiments, an increase in the coronary flow was recorded. In one experiment, the increase in

the flow was 100 percent, whereas in other experiments the increase was of the order of 50, 30, 25 and 20 percents, and in each case lasted for 30-60 minutes after a single injection. A second injection was usually ineffective. There was an increase in the coronary flow with compound H-475 in all four experiments. The increase over the basal flow ranged between 10-20 percent and lasted for approximately 20 minutes. The mean values of increase in coronary flow with the other compounds were as follows : H-810 and H-1000 (14 percent) and H-799 (10 percent). The flow returned to control levels in 10 minutes time.

Action on peripheral blood vessels

The action of some of these compounds was studied on the hind limb perfusion set up of the rat (Table II).

TABLE II

Action of nor camphane derivatives on peripheral blood vessels of the hind limb of the rat

Compound	Increase in flow (percent of basal value)					
	1 Min.	3 Min.	5 Min.	10 Min	25 Min.	20 Min.
Sodium Nitrite	12	20	16	12	4	0
H-610	12	40	52	28	20	12
H-475	16	28	28	24	24	16

On continuous infusion, Sodium nitrite, Comp. H-475 and Comp. H-610 produced an increase in flow which was maximal in 3-5 minutes time, and was near normal in 20 minutes.

Other experiments

It has already been reported that the compound H-610 produced marked stimulation of motor activities in small laboratory animals (3). The substitute compounds on injection to groups of 6 rats or 6 mice in a fixed dosage of 15 mg/kg did not produce any apparant change in behaviour. A gross action of these compounds on the systemic blood pressure of the dog was also studied. It has already been reported that the compound H-610 produces a depressor response due to cardiac depression (4). The compounds H-475 actually produced a transient rise in blood pressure lasting for 2-3 minutes. The other compounds produced transient depressor responses followed at times by a pressure effect (Fig. 5). The compound H-610 produces a small contraction of spleen of the dog (3). The compound H-475 produced marked contractions of the spleen of the dog in 2 experiments, when given in a dose of 10 mg 1 kg body weight.

DISCUSSION

All these compounds produced coronary vasodilatation in the isolated rabbit heart. The increase in the flow could have been due to a reduction in myocardial contractility (Fig. 4).

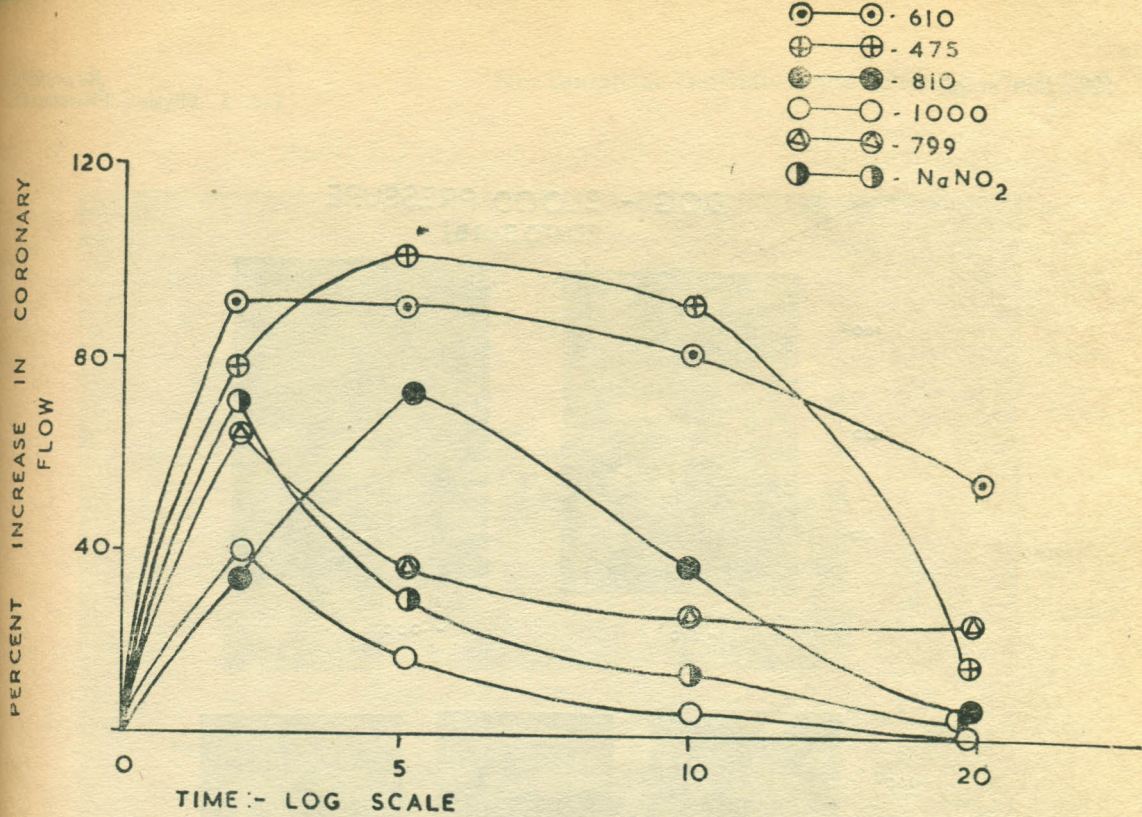


Fig. 2

MAXIMUM INCREASE IN CORONARY FLOW
AFTER NORCAMPHANE COMP.

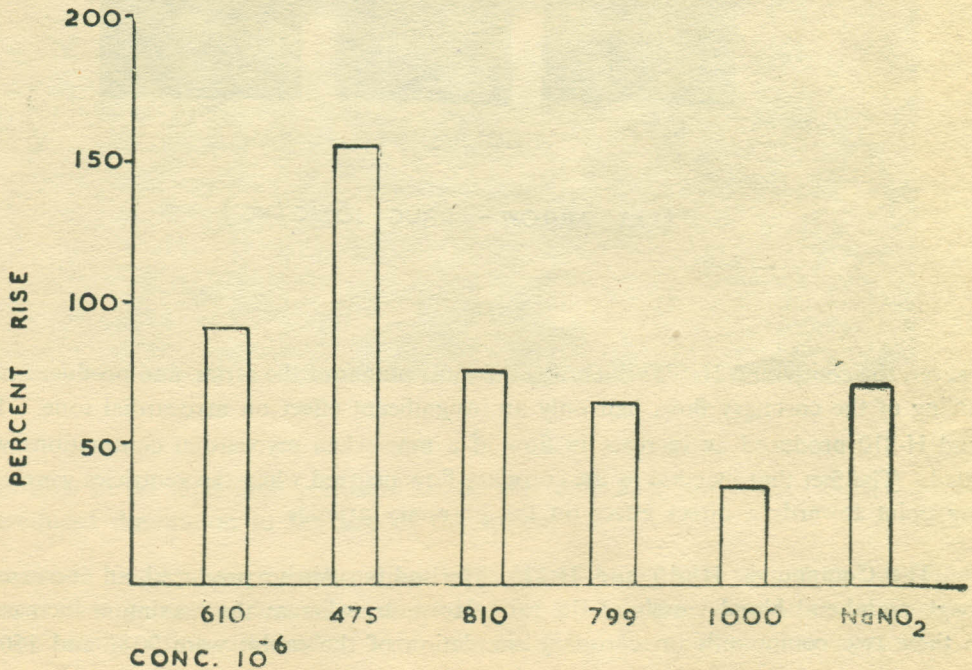


Fig. 3

RABBIT HEART - LANGENDORFF

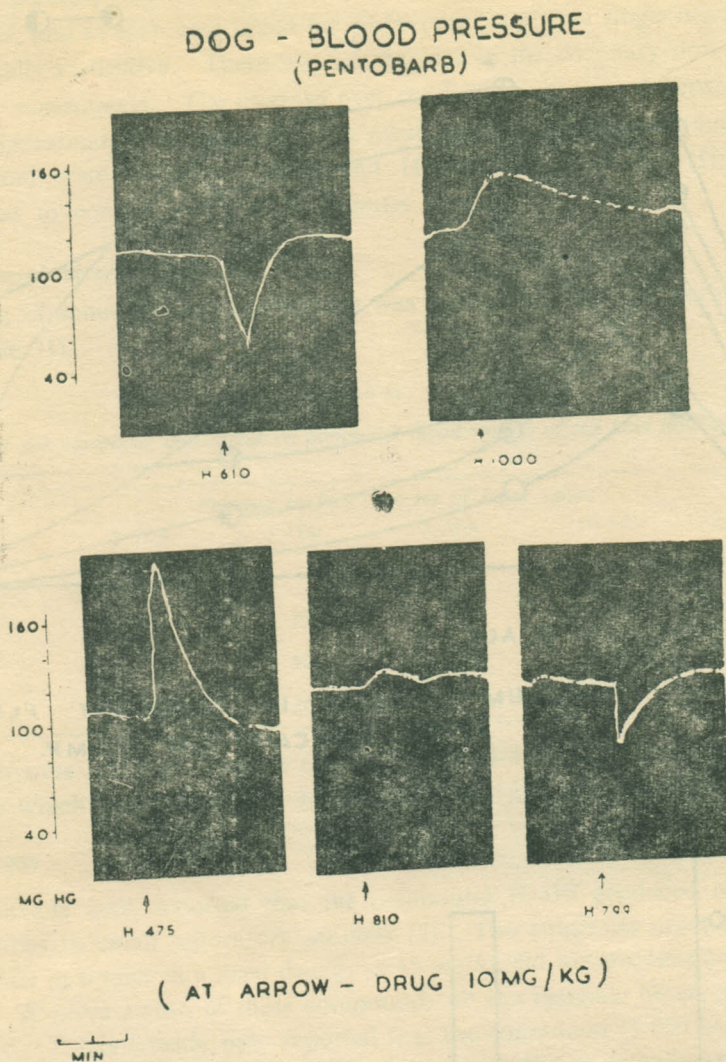


Fig. 4

However, the compound H-475 which was the most potent of the series, and produced more than doubling of the coronary flow, had only an insignificant effect on myocardial tone. The compound H-810 produced an increase in flow at a time when myocardial contractions were augmented. The fact that increase in the coronary flow occurred when the ventricles were also fibrillating points towards a direct effect on the coronary arteries.

The Compounds H-610 and H-475, like sodium nitrite produced an increase in flow through peripheral blood vessels of the rat. However, whereas the maximum increase in flow with these two compounds on coronary circulation of the rabbit were 90% and 150%, the

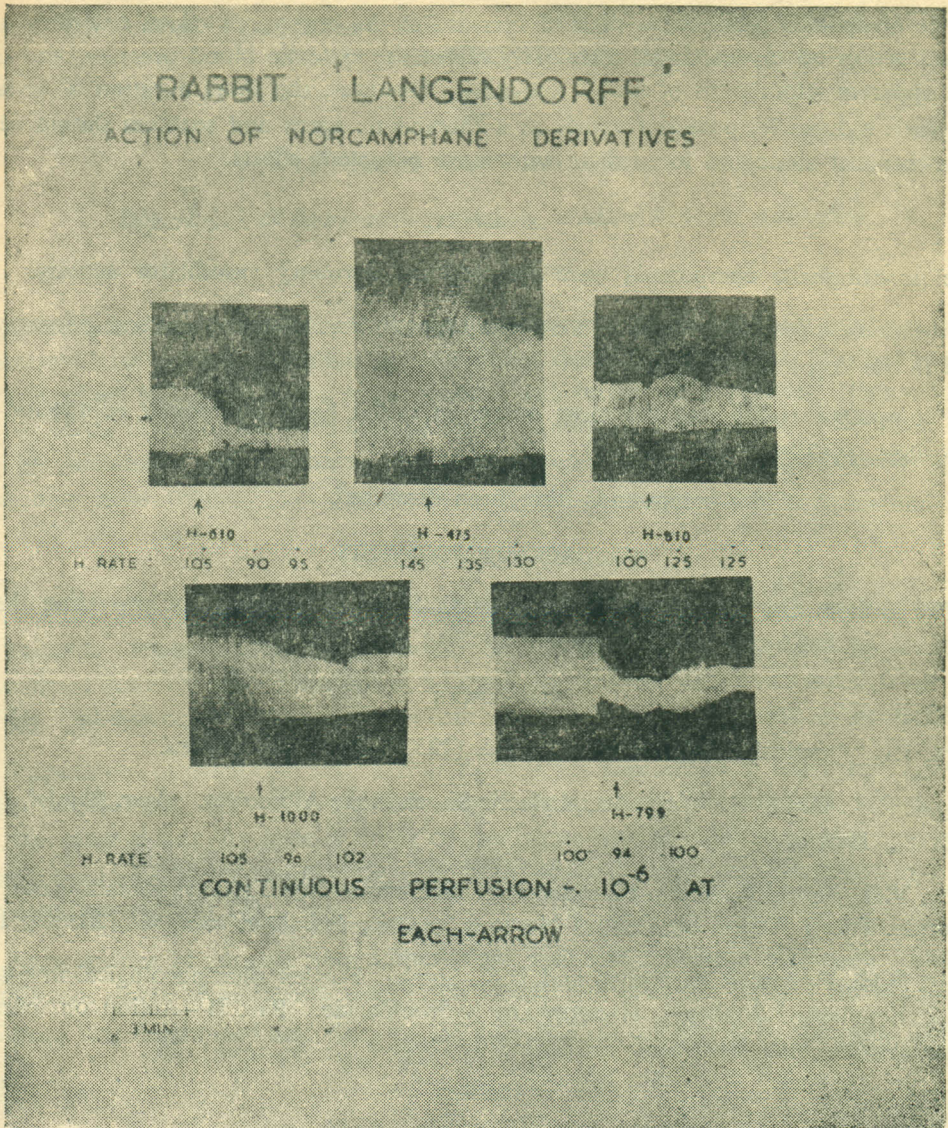


Fig. 5

increase in flow in rat hind limb perfusion set up was only 52% and 28%. Both these compounds produced diminution in the size of the spleen.

The rise in blood pressure produced by H-475 cannot account for the increase in coronary flow. The pressor phase was immediate and lasted for 2-3 minutes, whereas the maximum increase in the coronary flow occurred in 5 minutes and lasted for another 10 minutes.

The compound H-475 was thus the most promising compound of the series.

The compound produced a marked increase in the coronary flow, had only a slight depressant action on myocardium, transiently raised the systemic blood pressure, and did not produce apparent stimulation of motor activities. However, the short duration of action and tachyphylaxis reduces its potential values as a therapeutic agent and searches should be made amongst chemical analogues for a drug with more persistent effects.

SUMMARY

1. Five norcamphane compounds were screened for coronary vasodilator activity.
2. All compounds produced increase in coronary flow in the isolated rabbit and guineapig heart and in the dog heart *in vivo*.
3. The compound H-475 was the most potent in rabbit heart but parent compound H-610 was most effective in the dog.
4. The limitations of the compounds have been discussed.

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