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The Effects of Nikethamide on the Blood Pressure after Paralysis of the Autonomic Ganglia with Hexamethonium Chloride.

By

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Intravenous injection of a sufficient dose of nikethamide into animals produces an initial transient fall in the blood pressure and then an increase of fairly long duration. This was first reported by UHLMANN (1924) and has since been confirmed by many investigators (STROSS 1928; JUNKMANN and STROSS 1928; MASSART 1930; REGNIER and DE VLEESCHOUVER 1935; MYERS 1940; HAHN 1941). The intensity of the response to the drug varies with the anaesthetic agent and with the depth of anaesthesia, as well as from one species of animal to another. As a rule the effect consists of two stages, an initial decrease and a subsequent increase of the blood pressure. This observation has received the attention of many investigators and attempts have been made to find out where nikethamide acts in the organism to produce these effects.

UHLMANN (1924) did not analyse the depressant effect but suggested that the pressor effect is only partly of central origin (vasomotor centre), it being possible to produce a considerable pressor effect in cats even after transection of the cervical spinal cord. He ascribes the rest of the effect to the direct action of the drug on the vessels or to improved cardiac activity. He bases this view on the observations that nikethamide at a concentration of 1 : 1000—1 : 10 000 contracts the vessels of the isolated rabbit-ear and that nikethamide exerts a positive inotropic effect on frog and mammalian heart, whether isolated or *in situ*.

MASSART (1930), who studied the question extensively on dogs, concludes that the transient decrease in blood pressure is ascribable to a failing heart. In contrast with UHLMANN, he points out that nikethamide exerts a transient negative inotropic effect on the isolated dog-heart, provided that the concentration is sufficiently high. He also claims that nikethamide exerts a vasodilating effect by its direct action upon the vessel wall, as demonstrated by NOLF's three manometer method. He

also claims likewise, on the basis of these experiments, that the pressor effect is of central origin. As the pressor effect can also be produced in curarized animals, it cannot be ascribed to convulsions.

STROSS (1926) reported that the pressor effect could not be produced in decapitated rabbits and therefore concludes that it must be of central origin. However, VAN ESVELD (1930) demonstrated it in decerebrate cats.

ZINNITZ and VON BERGMANN (1936) reported that nikethamide produces a transient decrease in the blood pressure in Dale's spinal cats and therefore argue that its effect is not only central but also peripheral.

That the pressor effect of nikethamide is not ascribable to a direct action on the heart is claimed as established by many investigators, such as TRENDELÉNBURG (1929), LEYKO (1929) and GREMELS (1930, 1931). They are of the opinion that the pressor effect is due to stimulation of the vasomotor centre.

In a comprehensive monograph HILDEBRANDT (1937) stresses that the effect of nikethamide on the circulation is elicited through stimulation of the vasomotor centre and that it does not exert any peripheral effect on the heart. Neither is it capable of exerting a peripheral effect at the concentrations attainable in the organism.

MYERS (1940) made an extensive investigation of nikethamide, including a study of its effect on the circulation. He claims that the transient depression is due to a peripheral effect on the vessels, because perfusion of limb vessels even with low concentrations of nikethamide produced a transient vasodilatation and then a distinct vasoconstriction. He believes the pressor effect to be due partially to this constriction but to be mainly of central origin, because nikethamide produced no demonstrable effect on the blood pressure in animals in which the brain and the medulla oblongata had been removed or in which the medulla oblongata and the spinal cord had been destroyed. Neither was any increase seen in blood pressure after paralysis of the ganglia with nicotine tartrate. The effect of nikethamide on the isolated heart *in situ* was negligible.

In contradistiction with MYERS, HAHN (1941 a and b) has demonstrated that cats, even after decapitation, react to nikethamide with an initial transient decrease and a subsequent increase in blood pressure. Curarized animals, therefore in absence of convulsions, also react in the same manner. He considers that the increase must be ascribed to stimulation of the vasomotor centres of the spinal cord. In his opinion the depression is of peripheral origin, because it can be produced after section of the vagus and elimination of the pressor receptors of the carotid sinus.

HAHN and SIMON (1948) presented further evidence favouring the peripheral origin of the depressor effect. Nikethamide, though in concentrations as high as 1 : 1500, had a relaxing action on isolatid carotid

strips, and a concentration of 1 : 15000 distinctly decreased the sensitivity of the vessels to adrenaline.

HAHN, PLESTER and RUMMEL (1951) injected nikethamide into cats. either intravenously or directly into the vertebral artery, and showed that in the latter event the decrease in blood pressure was much greater, while in rabbits injection by either route produced an increase. They therefore claimed that the decrease cannot be of peripheral origin.

The literature thus contains a number of contradictory results, and it is obvious that the underlying mechanism of the action of nikethamide on blood pressure is still obscure.

In the present study an attempt was made to investigate the mode of action of nikethamide on blood pressure with the aid of ganglionic block produced by a hexamethonium salt.

Methods.

Rabbits and cats of either sex and weighing on the average 2.5 kg and 3.0 kg respectively were used. The animals were anaesthetized with urethane (1.75 g/kg body-weight). Heparin (5 mg/kg) was employed as an anti-coagulant. The blood pressure was measured by means of a mercury manometer connected to the right carotid artery. The injections were made into a femoral vein. The right vagus was sectioned in order to permit faradic stimulation of the peripheral end.The nikethamide used was *injectabile nicethamidi* (Swedish Pharmacopoeia), *i. e.* a solution containing 250 mg/ml. In order to obtain a suitable blood-pressure response under the above mentioned experimental conditions a dose of 50 mg/kg, *i. e.* 0.2 ml/kg was injected.

Ganglionic block was induced by hexamethonium chloride, 10—20 mg/kg, in 5% solution. When faradic stimulation of the peripheral end of the vagus failed to produce any blood-pressure response, it was taken as a sign that ganglionic block was complete.

Results.

Intravenous injection of 50 mg/kg body-weight nikethamide in rabbits anaesthetized with urethane immediately produced a marked, transient decrease in the blood pressure and then an increase varying in amount from animal to animal, but of fairly long duration, after which the pressure gradually returned to initial level (fig. 1). In a few animals, only a transient depression was recorded without any subsequent increase. After the injection of hexamethonium chloride, 10 mg/kg, the blood pressure dropped regularly down to a level of about 30 mm Hg and then gradually rose to about 50 mm Hg, at which level it persisted. In this respect rabbits seem to differ from cats (cf. PATON and ZAIMIS 1951), in which the pressure rapidly falls to the level (60—80 mm Hg) at which it stabilizes.

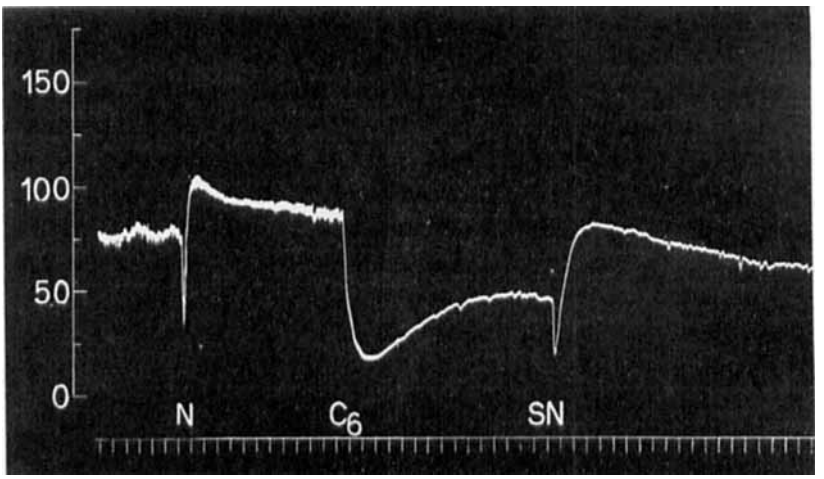

Fig. 1. Rabbit, 2.3 kg. The effect of nikethamide before and during paralysis of the autonomic ganglia by hexamethonium chloride. S = faradic stimulation of the vagus, N = nikethamide, 50 mg/kg, C_6 = hexamethonium chloride, 10 mg/kg. Time interval: 1 min.

Stimulation of the peripheral end of the vagus before blockade gave a momentary, marked decrease in the blood pressure. During blockade, stimulation of the vagus produced no demonstrable effect.

When hexamethonium chloride was administered in doses so large that the blood pressure no longer reacted to vagal stimulation, a further dose of 50 mg/kg nikethamide was injected. In all 19 animals the blood pressure again showed a momentary fall to the same level as, or still lower than, before the blockade and then an increase of fairly long duration (fig. 1.). In most animals in which nikethamide produced no increase before blockade but only a transient decrease, the blood pressure increased markedly after the blockade.

Discussion.

The effects of intravenous injection of nikethamide into rabbits anaesthetized with urethane confirm earlier observations that nikethamide produces a transient decrease in the blood pressure and then an increase of fairly long duration, but varying in amount from one animal to another.

The same effect is also elicited after ganglionic paralysis of the autonomic ganglia with a hexamethonium salt, though the increase recorded is as a rule much more pronounced.

In view of the general opinion that the pressor effect of nikethamide is of central origin, this observation is remarkable. Attention was there-

fore directed to the ganglionic block to see whether it had been sufficiently intense.

PATON and ZAIMIS (1949, 1951) report on the basis of careful investigation that in the cat hexamethonium iodide at doses of 0.2—2.0 mg/kg produces an decrease in the blood pressure down to a level of 60—80 mm Hg. Larger doses produce no further decrease in the blood pressure, but only an increase in the duration of the fall. PATON (1951) and PATON and ZAIMIS (1951) also report that hexamethonium salts do not block all autonomic ganglia to the same extent. The parasympathetic ganglia of the salivary gland seem to be the most sensitive, then the superior cervical ganglion, the vasomotor ganglia and the visceral ganglia and the vagal ganglia in the heart, in that order.

The dose used in the above mentioned experiments was 10—20 mg/kg of hexamethonium chloride, and was thus a fairly heavy one, especially as it was in the form of chloride and not iodide, which was used by PATON *et. al.* (A quantity of 10 mg chloride corresponds to 16.8 mg iodide.) For further control one experiment was also performed with hexamethonium chloride, 40 mg/kg (corresponding to 67 mg/kg iodide), with the same effect as with smaller doses (fig. 2).

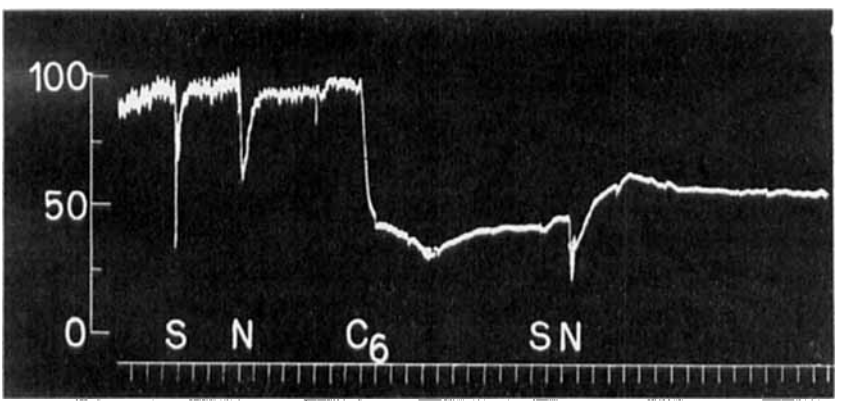

Fig. 2. Rabbit, 2.7 kg. The effect of nikethamide before and during paralysis of the autonomic ganglia by hexamethonium chloride. S = faradic stimulation of the vagus, N = nikethamide, 50 mg/kg, C_6 = hexamethonium chloride, 40 mg/kg. Time interval: 1 min.

As the blood pressure became steady at a level where further administration of hexamethonium chloride was not followed by a further fall and as faradic stimulation of the peripheral end of the vagus produced no response at all, the blockade must have been as complete as can be expected with the drug. As PATON's *et al.* data refer to cats, three control experiments were carried out on cats. The observations were the same as in the experiments on rabbits (fig. 3).

It may be concluded from these results that the intravenous administration of nikethamide, despite paralysis of the autonomic ganglia by hexamethonium chloride, continues to exert the same typical effect on the blood pressure as before the blockade. This is possible either because the effect is of peripheral origin or because it is elicited centrally by pathways that do not pass the synapses of the autonomic ganglia or pass by synapses completely resistant to hexamethonium chloride.

HAHN's *et al.* evidence for the depressant component being of central origin because of the occurrence of a more pronounced decrease of blood pressure after a given dose of nikethamide into the vertebral artery than

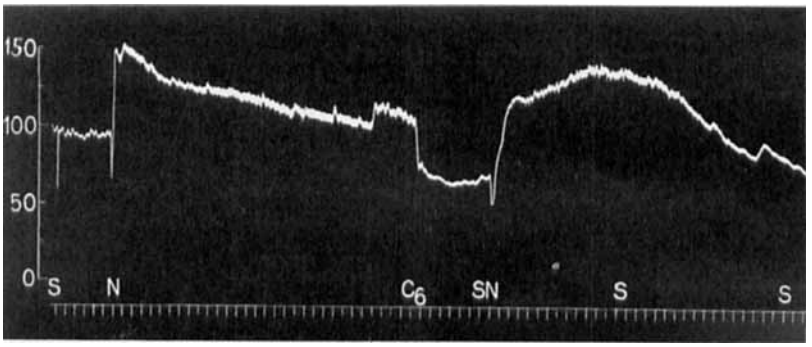

Fig. 3. Cat, 3.0 kg. The effect of nikethamide before and during paralysis of the autonomic ganglia by hexamethonium chloride. S = faradic stimulation of the vagus, N = nikethamide, 50 mg/kg, C_6 = hexamethonium chloride, 10 mg/kg. Time interval: 1 min.

when administered intravenously is not quite conclusive. On injection into vertebral artery the nikethamide probably reached the medulla oblongata at a much higher concentration than when administered intravenously and could then give rise to non-specific reactions.

The results of the experiments described above are in contrast especially with MYER'S (1940) investigations on urethane anaesthetized cats, in which the autonomic ganglia were paralysed with nicotine tartrate. In these experiments he recorded about 15 mm increase in the blood pressure before, but no increase during, the blockade. The depressor effect is not mentioned. In addition to the fact that MYERS used low concentrations of nikethamide it should also be pointed out that nicotine is not only a ganglionic blocking agent; it first produces a stimulation. Moreover it exerts a central effect and an effect on neuromuscular transmission, all effects that, practically speaking, hexamethonium chloride does not produce.

In addition PATON and PARRY (1951) and PATON (1951) report a distinct difference between the ganglionic blocking effect of nicotine and hexa-

methonium salts. Nicotine exerts its effect by depolarization, while hexamethonium salts produce a block by competition. The possibility that nikethamide produces its blood-pressure effects by direct action on the ganglionic cells cannot be excluded; if so, it would have no effect when block is produced by depolarization but would still exert its action despite the fact that hexamethonium by competitive block had made it impossible for acetylcholine to exert any effect.

Summary.

The effects of intravenously injected nikethamide on the blood pressure were studied both before and during paralysis of the autonomic ganglia with hexamethonium chloride. In both conditions nikethamide produced its typical effects on the blood pressure: a transient decrease followed by an increase of fairly long duration.

The possible sites of action at which nikethamide produces its effects on the blood pressure are discussed in relation to the results reported.

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