NEO-SYNEPHRIN: SOME USES AND EFFECTS IN OPHTHALMOLOGY*

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The sympathomimetic compound, neo-synephrin hydrochlorid, has properties of interest to ophthalmologists. After three years of clinical trial and some animal experimentation, a report is given under the following headings: I. Chemical and Physical Nature of the Preparation. II. General Action. III. Local Action. IV. Some Uses in Ophthalmology.

I. *Chemical and Physical Nature of the Preparation.*—According to the manufacturers, levo-meta-synephrin has an optical rotation of $-55.33°$ at 20° C. The melting point of the levo-hydrochlorid is 139° to 141° C. The levo-isomer of meta-synephrin (meta-methylaminoethomolphenol hydrochlorid) is an organic compound in the form of a white, crystalline powder, with one OH group in the meta position.

$$CH(OH).CH_2.N\begin{matrix}CH_3\\H\end{matrix}.HCl.$$

It has a high stability, and boiling with alkalis for a number of hours has not disturbed its properties. It is easily soluble in water.

II. *General Action.*—There have been a considerable number of reports upon the general action of the drug. In rather small doses the blood-pressure is raised and sustained over a considerable time (fig. 2). A dose of 1 mg. will produce, in a few minutes, a sustained rise of blood-pressure whether given intravenously (immediate effect), subcutaneously, intramuscularly, or through the cornea. In atropinized cats the pressor ratio of the hydrochlorid salt to epinephrin chlo-

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rid is as 4 is to 3 (Tainter and Stockton[1]). The mechanism of the pressor action is said to be both musculotropic and neurotropic (Tainter and Stockton[1]). The drug is not so strong a bronchodilator as epinephrin hydrochlorid, its ratio to epinephrin being 20: 4 (Tainter, Pedden, and James[2]). Nathanson[3] found a ratio of 1: 100 between epinephrin and neo-synephrin in induced cardiac standstill. Animal studies have shown an increase in the blood sugar following its use; also an increase in the secretion of saliva and of urine has been demonstrated (Geiter[4]). The lethal dose in animals is comparatively high. The toxicity varies with different species. The minimal lethal dose of ephedrin sulphate and epinephrin chlorid is much smaller than that of neo-synephrin chlorid. The minimal lethal dose by oral administration in rats is 0.7 to 0.8 gm. per kilogram; in rabbits, 0.015 to 0.025 gm. per kilogram; in pigeons, 2.45 gm. subcutaneously, or 0.0333 gm. intravenously per kilogram (Geiter[4]). Barger and Dale[5] have shown that the sympathetic stimulation by substances like epinephrin increased with the chemical resemblance to that substance, but that other effects than the pressor reactions were not necessarily consistent. According to animal studies, neo-synephrin does not diminish allergic reactions.

III. *Local Action.*—(1) The preparation has a marked decongestive effect. Tainter and Stockton[1] demonstrated in rabbits an anti-edema effect of neo-synephrin after a subcutaneous injection which produced a lessened reaction to mustard oil applied in the conjunctival sac as compared with controls. The writer has observed the above, and also a similar delay in reactions by two other routes. After both subconjunctival injections of 0.5 per cent. neo-synephrin and its topical application (1 per cent.), a delay and a diminution in reaction from conjunctival application of powdered ethylmorphin (dionin) have been observed. Slit-lamp examinations of the limbic vessels showed a markedly sustained vasoconstrictor effect from topical or subconjunctival injection of

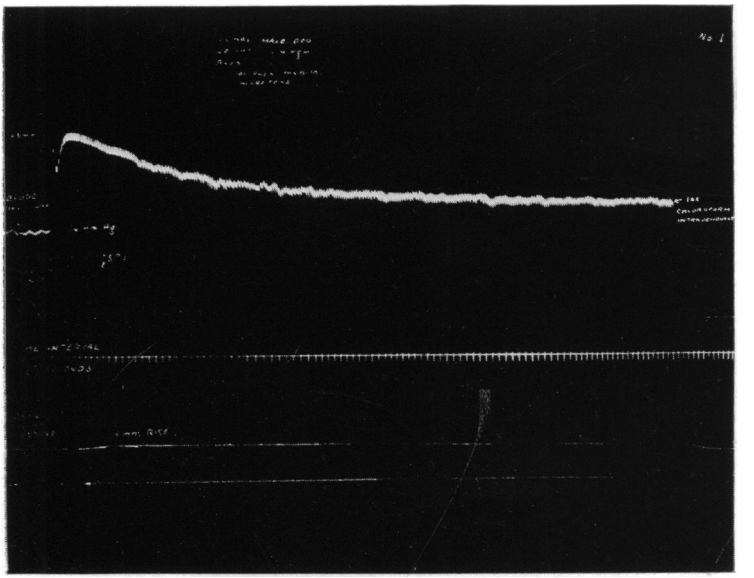

Fig. 1.—Effect of neo-synephrin hydrochlorid (intravenous route) on blood-pressure and intra-ocular pressure. Dog, 12.4 kilograms, 500 phenobarbital chloretone, mercury manometer record. Neo-synephrin hydrochlorid, 0.02 mg. (per kilogram). Blood-pressure abrupt rise 77 mm. Hg, intra-ocular rise 4 mm. Hg.

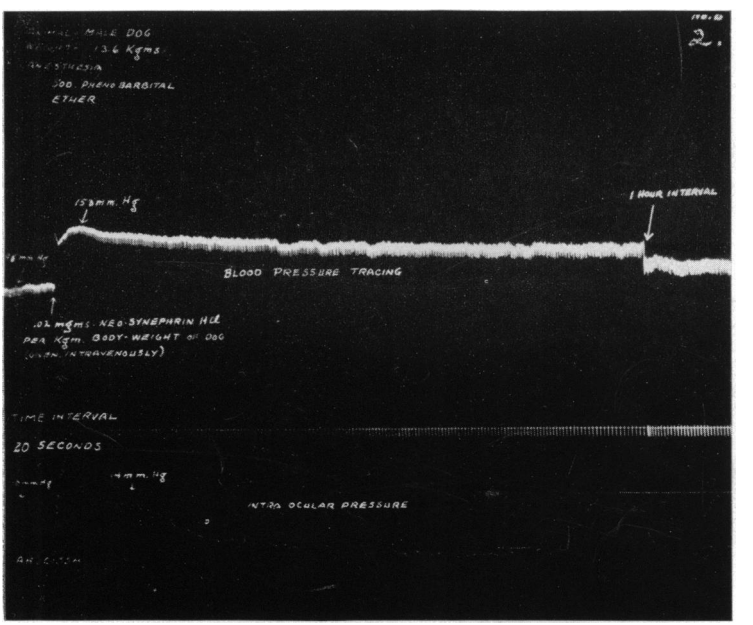

Fig. 2.—Effect of neo-synephrin hydrochlorid (intravenous route) on blood-pressure and intra-ocular pressure. Dog, 13.6 kilograms, 500 phenobarbital ether, mercury manometer record. Neo-synephrin hydrochlorid, 0.02 mg. (per kilogram). Blood-pressure abrupt and sustained rise, 58 mm. Hg to intra-ocular pressure 4 mm. Hg.

1 to 0.5 per cent. neo-synephrin. Constriction begins in from thirty to ninety seconds, and lasts from two to six hours.

(2) With the 1 per cent. solution the mydriatic effect is substantial. This varies somewhat, depending upon how the solution is applied, but the dilatation is fairly uniform if the solution is applied within a petroleum-jelly ring on the cornea. The effect is noted in approximately ten minutes, and lasts for a variable length of time following a single instillation. The dilatation is uniform in different segments of the iris, but varies as to degree. In a series of several hundred eyes those with intra-ocular tension in the higher brackets (25 to 29 mm. Hg Schiötz) dilated more widely than those with intra-ocular tension in the lower brackets (15 to 20 mm. Hg Schiötz). The pupil usually, but not always, reacts to light at the height of the dilatation. The dilatation lasts from ninety minutes to four and one-half hours. Some patients are especially susceptible, and in them the dilatation may last from six to eight hours. The latter group is very small. The dilatation of the iris is opposed by either eserin or pilocarpin, the first in 0.2 per cent. solution and the latter in a 1 per cent. solution. The decongestive effect may be elicited without dilatation of the pupil if neo-synephrin is combined with a myotic.

(3) The use of a 0.5 per cent. to a 0.75 per cent. solution in a single instillation has little effect on the accommodative power other than that ensuing from the dilatation of the pupil. Repeated instillation has a mild cycloplegic effect. The partial loss of accommodation is of short duration,—from two to ten hours,—and follows the instillation of from four to six drops. This effect is opposed by eserin or pilocarpin.

(4) A single topical application of a 0.5 per cent. to 1 per cent. solution did not cause an increase of intra-ocular pressure of a significant amount in a series of trials. In some patients the repeated instillation of from 4 to 6 drops of a 1 per cent. solution has produced a slight increase in intra-ocular

pressure. From intravenous use with a rise in blood-pressure (dosage 0.02 mg. per kilogram in dogs) there has been a coincident lesser rise in intra-ocular pressure, as shown in the curve (fig. 1). Pure neo-synephrin applied to the dog cornea (3 mg.) produces the marked rise in blood-pressure noted on the curve (fig. 4).

(5) Neo-synephrin will produce a pressor response in animals whose sympathetic nerve endings have been paralyzed after ergotamin. Accordingly it is believed that the compound acts upon both the myoneural junction and the muscle itself. It obviously stimulates the dilated fibers of the iris. The dilatating action on the iris produced by the topical application of 4 per cent. cocain is increased by further application of neo-synephrin.

(6) Interstitial injection of the compound, as in local anesthesia, produces a marked ischemia and almost doubles the time of the local anesthesia of novocain. In this regard it is about two-thirds as strong as epinephrin (1:1,000). From two to four minims of a 1 per cent. neo-synephrin solution were added to 2 c.c. of a 1 per cent. procain solution (fig. 3). No side effects have been noted as in the use of epinephrin.

IV. *Some Uses in Ophthalmology.*—Neo-synephrin would seem to have definite advantages in practical use by the ophthalmologist.

(1) For decongestion or as a vasoconstrictor, 0.125 per cent. to 0.25 per cent., or 0.5 per cent. to 1 per cent. with 0.125 per cent. to 0.25 per cent. pilocarpin, instilled in the conjunctival sac.

(2) To dilate the pupil for intra-ocular examination, a 0.75 per cent. to 1 per cent. solution, one instillation, 1 minim (1 minim = 0.66+ mg.).

(3) To prolong local anesthesia and to reduce hemorrhage in the operative field, 1 per cent. procain and 0.025 per cent. to 0.03 per cent. neo-synephrin.

(4) To dilate the shrinking pupil in uveitis, a 1 per cent. solution may be used with atropin applied to the cornea. The

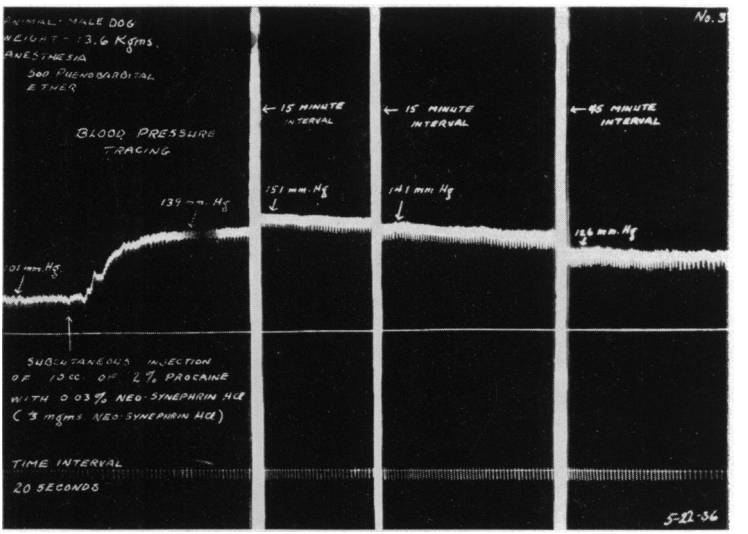

Fig. 3.—Effect of neo-synephrin hydrochlorid (subcutaneous route, as in local infiltrative anesthesia) on blood-pressure. Dog, 13.6 kilograms, 500 phenobarbital ether, mercury manometer record. Ten c.c. of 2 per cent. procain with 0.03 per cent. neo-synephrin hydrochlorid (3 mg.). Blood-pressure rise more gradual, 55 mm. Hg, and long sustained

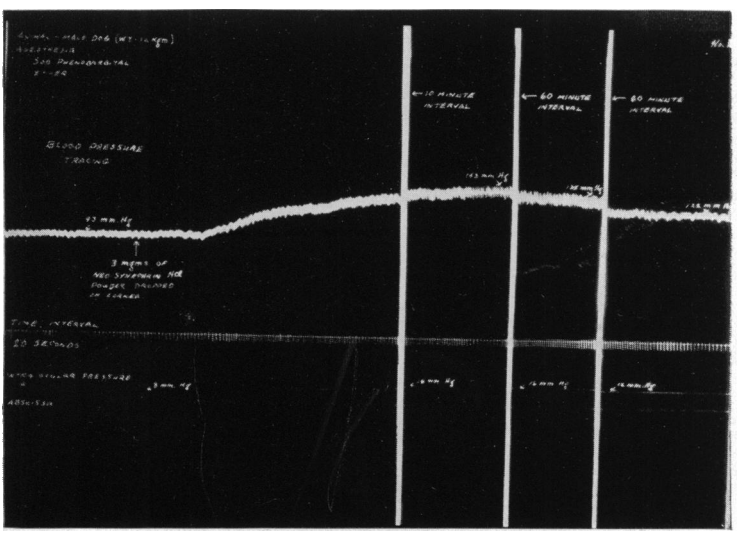

Fig. 4.—Effect of neo-synephrin hydrochlorid (through cornea route) on blood-pressure and intra-ocular pressure. Dog, 12 kilograms, 500 phenobarbital ether, mercury manometer record. Three mg. powdered neo-synephrin hydrochlorid. Blood-pressure rise, 50 mm. Hg, intra-ocular rise, 8 mm. Hg, both gradual and sustained.

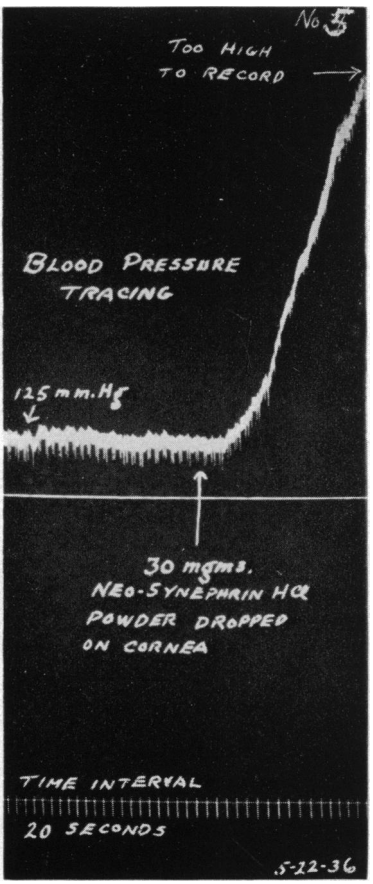

Fig. 5.—Showing abrupt rise in blood-pressure in a dog from 30 mg. neo-synephrin hydrochlorid powder applied to the cornea. Time intervals, twenty seconds. Mercury manometer recording limit reached.

writer has used pure neo-synephrin powder (1 mg.), applied above the limbus to break synechiae, with considerable success, providing the adhesions have not been of too long standing. This method has broken synechiae and given round pupils that have been resistant to the repeated use of 2 per cent. atropin and epinephrin, 1:1,000 solution. No untoward actions have been noted in six cases of severe uveitis in which the powdered form was used. In view of the experimental sharp rise of blood-pressure from the application of the pure drug on the cornea, its use in this strength should be limited with great care to active uveitis in patients not afflicted with either severe arteriosclerosis or hypertension (fig. 5).

(5) The drug has some value in a few selected cases for classifying patients with high border-line intra-ocular pressures. Following dilatation with neo-synephrin by placing one drop of a 1 per cent. solution on the cornea (it may be quickly overcome by a myotic), a significant rise in pressure would indicate a preglaucomatous state in the patient. Contrariwise, a significant fall of intra-ocular pressure would suggest that the suspected glaucoma was of the secondary type. The classification is not so simple as it seems here, since a number of factors are involved, particularly the state of the capillary bed and the structure of the filtration angle.

(6) The hemodynamic quality of this substance is of value in the treatment of shock and has been used clinically by Johnson.[6] The dosage is, intravenously, 0.5 to 1 mg. with physiologic salt solution, or subcutaneously, 5 to 10 mg.

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