TREATMENT OF THE HYPOTENSIVE STATES OF SPINAL ANALGESIA WITH DILUTE NEOXYNEPHRIN SOLUTION *

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Received for publication November 10, 1950

Spinal analgesia is efficacious because it produces paralysis of motor fibers with profound muscular relaxation and blockade of transmission of nerve impulses over sensory fibers. Sympathetic fibers also are paralyzed and this effect actually is undesirable.

Physiologically, a significant aid in the normal maintenance of blood pressure is the alternating constriction and relaxation of blood vessels throughout the body. Constriction or dilatation takes place in one region to compensate for the inverse actions of dilatation or constriction in other areas. The sympathetic outflow of the autonomic nervous system governing these functions is confined to the spinal segments of the first thoracic through the second lumbar vertebrae. During spinal analgesia for abdominal surgical procedures the majority of these segments are paralyzed. Those that remain functional are able to compensate for the inactivated ones and thereby maintain blood pressure at near normal values if the mechanism is highly efficient as in the young adult and if the intact segments are of sufficient number. These factors are variable and predictable only in a general way.

The prophylactic use of ephedrine and related compounds having a moderate but rather prolonged vasopressor action has increased the number of individuals in whom blood pressure changes are minimal during spinal analgesia. There remain the unpredictable cases in which blood pressures fall precipitously or steadily to levels incompatible with satisfactory cardiovascular function. In these, the effects of supplemental doses of ephedrine are neither prompt nor dependable. Owing to the well established property of tachyphylaxis, it is difficult or impossible to estimate the effect of any given dose. Effects too little or too great are the rule.

Neosynephrin administered subcutaneously and intramuscularly as a prophylactic vasopressor in spinal analgesia has been described many times (4, 5, 6, 11) but its employment has not gained general acceptance.

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The longer acting sympathomimetic drugs producing a less marked and more sustained vasopressor action when administered intramuscularly remain in favor for prophylaxis. They prove adequate in the majority of cases selected for spinal analgesia. Dilute solution of neosynephrin hydrochloride administered by continuous intravenous infusion is proposed further to sustain blood pressure when needed. Its use in this manner widens the scope of spinal analgesia because it provides a certain and easily controlled technic of raising and maintaining blood pressure in the event of peripheral vascular inadequacy or collapse.

**Pharmacology**

While the chemical structure of neosynephrin is quite similar to that of epinephrine, ephedrine and other sympathomimetic amines, its administration evokes certain pharmacodynamic actions which are quite advantageous in comparison to the effects of other members of this group of drugs.

The pronounced vasopressor action which it exerts is of chief interest in the present report. The rise of blood pressure which follows the intravenous administration of neosynephrin is practically as rapid as that produced by epinephrine and the duration of the rise is several times as long. Diastolic pressure is elevated before there is a response in the systolic pressure (9), the effect being due to the peripheral action of the drug on smooth muscle in the walls of the blood vessels (4). There is no "postdilatation effect" with neosynephrin—the fall of blood pressure below the initial level which occurs almost routinely as the final phase of action of epinephrine.

Associated with the consistent elevations of pressure which are produced by successive administrations of neosynephrin, there usually is a bradycardia which apparently is produced by reflex vagal action on the sino-auricular node (15). Atropine abolishes the bradycardia and even permits mild tachycardia (13). Both the systolic and diastolic size of the heart are increased, and the total work it performs is increased (13). The stroke volume is increased but in consequence of the bradycardia the minute volume does not change appreciably (10). Total oxygen consumption is the same during the bradycardia, and coronary flow in animals has been shown to increase subsequent to dilatation of the coronary vessels (13). A similar coronary effect is considered to occur in man (8). Circulation time is slightly increased and so is venous pressure (13). Cerebral circulation is accelerated and a consequent increase in oxygen content of venous blood is evident (14).

Electrocardiographic changes resulting from administration of neosynephrin are minimal and not of serious importance (9, 13, 18). There is, of course, a slowing of rate and a slight increase, within normal limits, of the P-R interval. Conduction times remain unchanged. Slight changes in height of the P and T wave have been reported. Most significant, from an electrocardiographic standpoint, is the extreme infre-
quency of irregularities. Those which do arise are never from the more dangerous ventricular centers. Even large doses of 5 to 10 mg. of neosynephrin injected subcutaneously into patients with damaged hearts failed to arouse irregularities (2).

Equipressor amounts of neosynephrin compared to epinephrine caused no cardiac irregularities, in contrast to the potentially dangerous ventricular tachycardia aroused in the dog by the latter drug in the presence of cardiac sensitizing general anesthetic agents (7). Dosages of neosynephrin four times as great in blood pressure raising action, when compared to epinephrine, aroused only auriculo-ventricular nodal rhythm in the experimental animal. Similar auriculo-ventricular nodal rhythm has been the most serious type of irregularity produced by neosynephrin in clinical investigations (13).

There are other advantageous actions of neosynephrin which are not particularly pertinent to the present problem. Thus, the fact that there was no stimulation of the central nervous system was noted in a series of 163 patients studied by Brunner and de Takats (6). Neither was there alteration in sensitivity of the spinal cord to response of the knee jerk (2). Bronchiolar dilatation is produced by neosynephrin and a brief apnea is evident subsequent to its injection and the rise of blood pressure (12). No respiratory embarrassment is evident in human beings after its administration (10). Blood sugar is not altered by neosynephrin (1); it reflexly inhibits activity of the gastrointestinal tract; depressed tone and contractility of the uterus and has an antidiuretic action (12).

The outstanding favorable actions of the drug may be summarized as follows: (1) rapid and repeated vasopressor effect several times longer in duration than that of epinephrine; (2) no "postdilatation" phase; (3) no serious cardiac arrhythmias even when given in much greater dosages than the equivalent pressure-raising amount of epinephrine and (4) improved coronary and cerebral blood flow. If neosynephrin may be considered to possess any unfavorable property, it would be its 20 to 50 per cent potency, weight for weight, when compared with epinephrine. This factor can be controlled very easily, however, simply by giving more of the drug, that is, enough to accomplish the purpose for which it is chosen.

**Technic**

The purpose of administering dilute neosynephrin solution intravenously is to maintain blood pressure within the patient's usual range whether that be a so-called normal or a hypotensive or hypertensive state. Neosynephrin is a potent vasopressor drug and the complications incident to its use are related to overdose. The exact dose is unimportant as long as the amount used accomplishes the desired effect without undue complication. Through experience, general limits of dosage have been determined and will be described. Exceeding these
limits in either direction, however, may be necessary. The merit of the use of neosynephrin is the versatility of response in a consistent manner from minute to minute.

Neosynephrin hydrochloride, 10 mg, as a 1 per cent aqueous solution (1 cc.), is added to the intravenous solution already being administered. Having the neosynephrin in a syringe ready to add to the intravenous solution makes it possible to initiate the therapy within seconds. The solution may be 5 or 10 per cent glucose in water or saline or ½ molar lactate. Although compatible and stable in blood, neosynephrin is not added to it. This is due to the fact that the need for blood may change. The need for neosynephrin solution likewise is variable. Probably these two needs are not ever parallel. Blood containing neosynephrin may have to be slowed excessively to prevent an exorbitant rise in blood pressure at a time when blood replacement is imperative. The opposite may be true so that the blood is “wasted” or the circulatory system is overloaded.

In the hypotensive state of spinal analgesia neosynephrin solution, 10 mg, in 500 cc. (1: 50,000), usually will raise and maintain the blood pressure (fig. 1). The initial rate of administration is 100 to 180 drops per minute and this is reduced gradually to 40 to 60 drops for maintenance. When blood pressure does not respond to this procedure, a

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**Fig. 1.**

**Fig. 2.**

**Fig. 3.**
second 10 mg. is added to make a solution of 1: 25,000 or less. Such an addition is necessary when the blood pressure does not respond promptly (fig. 2) or the rise is inadequate or an excessive rate of flow (100 drops per minute or more) is necessary (fig. 3). Exceptionally, when fluid intravenously in quantity is contraindicated, a solution of sufficient potency is used so that the rate can be slowed to 6 to 20 drops per minute and still maintain the pressure.

The guide to the rate of administration is the blood pressure. The patient’s usual blood pressure based on readings taken in the physician’s office and at the hospital the day or so before the operation is noted. The blood pressure at the outset of anesthesia is recorded. After the spinal injection has been made and the patient assumes the supine position, a reading is taken at once. Readings are repeated at one to three minute intervals as convenient, while doing other tasks incident to the preparation for operation including the starting of intravenous fluids, checking the level of analgesia, placing the arms, placing shoulder braces and the like. If the blood pressure begins to fall, readings are taken at one minute intervals until the need for neosynephrin is decided or the blood pressure has stabilized at a satisfactory level. The latter is considered to be at a level within 20 per cent of the predetermined average of the individual based on the known readings. There may be exceptions in
the young healthy adult who may be expected to compensate in a relatively short time and in the meantime not to suffer deleterious effects from hypoxia. Many times adequate treatment is the immediate inhalation of almost 100 per cent oxygen. Such oxygen administration is always used with neosynephrin while the blood pressure is being stabilized.

Fig. 7.

Fig. 8.

Fig. 9.

The blood pressure response to dilute neosynephrin solution intravenously is often rapid and dramatic. Therefore, determinations are made every minute while the rate of flow is high. They are not charted as a rule but figure 4 illustrates a case in which it was done. Minute to minute determinations will prevent the inadvertent development of hypertension. Unless such detailed attention is given during this period, excessive levels of pressure are easy to attain (fig. 5).
The rising blood pressure lags, that is, when the rate of administration of the neosynephrin solution is slowed, the blood pressure may be expected to continue to rise for one to several minutes (fig. 4). Blood pressure readings are continued every minute after slowing the solution until the peak has been passed. Then readings are taken at two to five minute intervals depending on the case with which the maintenance rate of flow is determined.

As soon as the blood pressure of the patient is stabilized, five minute check-up determinations will suffice, except under certain circumstances, examples of which follow. As the spinal analgesia wears off and the paralyzed state of the sympathetics subsides, the need for neosynephrin solution gradually will decrease (fig. 6). Need for an increased rate of flow may be expected in fractional spinal analgesia after each dose of spinal drug. Change in position during or immediately following operation may affect the blood pressure adversely (fig. 7). Traction reflexes can affect the blood pressure similarly (fig. 8). Frequent determinations at these times will identify more quickly a fall in blood pressure and in each instance the solution is speeded for short periods.

In most cases at the termination of operation neosynephrin solution will have been discontinued. If not, postoperative orders include instructions to take the blood pressure every fifteen minutes, to keep the
blood pressure within specified limits by adjusting the rate of flow and to discontinue the solution as soon as the patient can move his legs. In the event that the blood pressure is not well maintained, a search for another cause of the hypotension is begun, preferably in consultation with the attending surgeon or internist. Further use of neosynephrin solution is then integrated with other forms of therapy directed to the total well-being of the patient, including blood pressure maintenance.

Two types of fall in blood pressure have been recognized. In figure 9 is illustrated the situation in which it drops gradually and continually without indication that compensation will take place. A critical level is selected and the neosynephrin solution started. In the precipitous type of fall illustrated in figure 10, when intravenous fluids have not yet been started, immediate treatment is to begin administration of oxygen by mask and coincidentally to place a tourniquet at the ankle. The latter is left in place while the neosynephrin solution is prepared so there will be sufficient time for filling of veins. In spite of the peripheral collapse venipuncture is relatively easy in the lower extremity providing the tourniquet is in place sufficiently long. Venipuncture in the arm is difficult, apparently because of compensatory vasoconstriction.

Complications

Any technic involving an effective drug implies toxic actions of overdosage. The usual therapeutic doses can become toxic when a pathologic state coexists.

*Hypotension.*—An inadequate response to the neosynephrin solution may occur because the concentration of the drug is too low. Experience with the method and an appreciation that dosage is subservient to the clinical response are necessary. An important safeguard is a knowledge that no other cause for the hypotension exists, and is one of the responsibilities when this technic is used. The degree of surgical trauma and blood loss is continually evaluated as a possible contributing factor to hypotension.

*Difficult Evaluation of Secondary Shock.*—Neosynephrin to raise and temporarily sustain blood pressure in the shock of trauma and hemorrhage has been recommended (3, 18). Because it is effective under these circumstances of hypotension, unusual care and attention are given to the evaluation of blood loss and trauma, remembering that the blood pressure can be at normal levels in spite of the existence of secondary shock.

*Hypertension.*—Figure 11 illustrates that hypertension can develop if close observation is neglected. That neosynephrin can raise the blood pressure beyond normal limits is a most logical reason for continuous intravenous administration. Experience with neosynephrin has caused agreement with Thomas (16) that "subcutaneous or intramuscular administration of sympathomimetic compounds is neither dependable nor predictable."
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Persistent Hypotension after Discontinuation.—There is no case in the 200 records available to indicate that the normal vasopressor action of the vessels is altered after neosynephrin. The possibility, however, is not without theoretical considerations. Close postoperative supervision is essential. Neosynephrin is used only when indicated.

Headache.—Unwanted hypertension is sometimes accompanied by headache (fig. 11). Apparently the hypertension need not be of a severe grade. In each of the 8 cases in which it was encountered, headache was of great intensity accompanied by restlessness and apprehension. In 4 cases the headache was occipital and in the other 4 migratory, beginning in the occipital region. Psychologically and therapeutically it is good practice in treating the headache to put the patient to sleep with pentothal sodium in addition to discontinuing administration of neosynephrin. If the usual sleeping dose of 100 to 240 mg. is given rather rapidly, the fall in blood pressure to near preoperative levels will be prompt.

Cerebral Accident.—In hypertension of neosynephrin, a cerebral accident may occur. Thomas (18) related his knowledge of such a case.

Bradycardia.—In the continuous intravenous method of administration, marked slowing of the heart rate is not a feature of the response in the cases in which blood pressures remain at or below the usual levels. At the time that administration of neosynephrin solution is started to correct hypotension, the pulse is increased above the usual rate. Also, the quality changes, the pulse being weak and of low volume, of a "thready" or "running together" character. As the blood pressure rises the rate tends to approach the previous value or remains but slightly below it and the quality becomes strong and full. If the facial skin color has been pale and shallow it becomes deep and full. Arteriolar capillary refilling is vigorous and prompt.

Heart Block.—Bradycardia has been so generally reported that with its occurrence heart block must be seriously considered. Brunner and de Takats (6) reported a case of partial heart block, but a dose of 10 mg. of neosynephrin in 1 cc. had been given intramuscularly. Thomas (18) listed heart block as a contraindication to the use of continuous neosynephrin solution. Figure 12 presents a case of heart block in which, all factors considered, spinal analgesia was the anesthetic procedure of choice. A severe drop in blood pressure occurred. Rather than risk the consequence of an uncompensated peripheral vascular inadequacy, neosynephrin was given. No essential change in heart rate occurred at any time.

Arrhythmias.—Orth et al. (7), in experiments with dogs, have concluded that despite the sensitizing effect of certain general anesthetic agents on the automatic tissues of the heart, the administration of neosynephrin does not elicit ventricular cardiac irregularities such as is common with most of the sympathomimetic amines. Clinically, irregularities have been reported infrequently and then only with large doses.
of neosynephrin. In fact, neosynephrin has been employed as an efficient drug to relieve distressing auricular fibrillation after other methods of treatment had failed (13, 17).

**Summary**

Dilute solution of neosynephrin hydrochloride administered by continuous intravenous infusion is proposed for the treatment of the hypotensive states of spinal analgesia.

The significant pharmacology of neosynephrin is reviewed.

The technic for the administration of dilute neosynephrin solution is given. Possible complications attending the method are enumerated and briefly discussed.

**REFERENCES**