THE EFFICIENCY OF OENETHYL (2, METHYL AMINO HEPTANE) AS A VASOPRESSOR SUBSTANCE FOR SPINAL ANESTHESIA *

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Vasopressor substances are the most effective therapeutic agents for combating the hypotension which so frequently accompanies spinal anesthesia. Aromatic amines, such as ephedrine, neosynephrine and propadrine, are used extensively and serve the purpose admirably as far as control of hypotension is concerned. However, they possess a variability of action and certain side effects which often cause another substance to be desired. Tachycardia, palpitation, dizziness, tremor, nausea, sweating, pallor and coldness of the skin are some of the objectionable features which curtail their clinical value. Recently, various aliphatic or straight chained amines have been introduced into therapeutics which possess a vasopressor action and cause responses suggestive of sympathetic stimulation. One of these, 2-aminoheptane, also known as tuamine, has been used as a vasoconstrictor in the nasal passages. Another, octin, or 2-methylamino-iso-octene, is spasmolytic for smooth muscle as well as a vasopressor. Still another, 2-methylaminoheptane or oenethyl, likewise, is pharmacologically related to tuamine and octin. Tuamine is a saturated primary amine; oenethyl, a saturated secondary amine, and octin, an unsaturated secondary amine (table 1). Barger and Dale (1), who first studied the aliphatic amines, found that sympathomimetic activity appeared in compounds having more than three carbon atoms. Maximum activity appeared in the six carbon compounds. Substitution of the amino group produced compounds of lesser activity.

Inasmuch as aliphatic amines have not been employed for overcoming the hypotension of spinal anesthesia, we have been interested in determining the clinical value of this type of compound for this purpose. This report includes experiences with oenethyl in 1,000 surgical patients. A preliminary report of its use in the first 100 patients has been published (2).

Chemistry and Pharmacology

The pharmacologic actions and clinical value of aliphatic amines, because of their relative newness, have not been studied in all their

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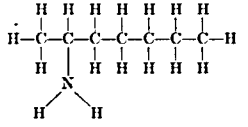
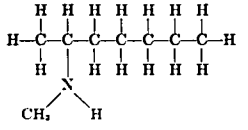
aspects. The pharmacologic action of 2-methylaminoheptane in experimental animals has been reported in some detail by Jackson (3) and also by Ahlquist (4). The drug is undergoing further study in other laboratories. It possesses many of the actions characteristic of epinephrine.

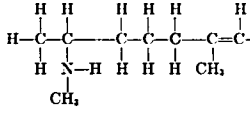
TABLE 1



2, Amino Heptane
Tuamine (Lilly).



2 Methyl Amino Heptane
Oenethyl (Bilhuber).



2 Methyl Amino Iso Octene
Octin (Bilhuber).

Oenethyl is a clear, colorless, volatile liquid which is slightly soluble in water. Saturated aqueous solutions are mildly alkaline since the drug is a base. A variety of salts forms when the base is neutralized with organic and inorganic acids. The salts are more soluble in water than the base. The substance is available in the form of the hydrochloride, benzoate and the mucate. At present, the drug is available for investigational use in 2 cc. ampules containing 100 mg. per ampule. When first released for investigation, it was designated as EA-1 hydrochloride. The name oenethyl hydrochloride has only recently been adopted.*

The vasopressor action both in man and animals in many respects is similar to that of epinephrine but is sustained over a much longer period of time. A consistent rise in both systolic and diastolic pressure is observed in dogs when 1 mg. per kilogram is given intravenously. An increase in pulse pressure occurs even though the diastolic pressure is elevated. The pressor effect decreases with each subsequent dose (tachyphylaxis). The pressor effect caused by oenethyl, as is the case with epinephrine, ephedrine, neosynephrine and many other vasopressors, appears to be due largely to constriction of the arterioles. In dogs, the heart is stimulated and there is an improvement in its con-

* Supplied through the courtesy of Bilhuber-Knoll Corporation, Orange, N. J.

tractions. The improvement in heart action results from stimulation of the sympathetic nerve endings and from a direct effect on the heart muscle itself. The drug does not have any significant action on the autonomic ganglia. Dilatation of the pupil, piloerection, and other manifestations of sympathetic stimulation are also observed after its administration, as is the case when epinephrine is given. Oenethyl possesses a bronchodilatory action. It also causes a decrease in renal volume. Some stimulation of respiration occurs when pressor doses are administered. It appears to have no action on the smooth muscle of the uterus. Doses sufficient to produce the pressor effect caused no notable electrocardiographic changes (5). Large doses (over 2.5 mg. per kilogram), however, caused changes in rhythm. Auricular tachycardia and ventricular premature beats were the more frequent arrhythmias. Disturbances of cardiac automaticity caused by the aromatic amines when used with cyclopropane did not occur when oenethyl was given to dogs under similar circumstances (6).

In dogs, the toxicity of oenethyl is low (2). In therapeutic doses, oenethyl does not appear to have any direct stimulating or depressing action upon the central nervous system. Nausea and vomiting are notably absent even after administration of large doses. With large doses, however, weakness, lethargy, drowsiness or prostration do appear. Toxic doses cause circulatory depression in dogs manifested by hypotension and depression of the pulse rate. The administration of oenethyl to a normal adult is followed by transient rise in blood pressure, a feeling of euphoria at first and then lassitude.

METHOD OF STUDY

The drug was administered whenever a vasopressor was indicated to all types of patients undergoing major and minor surgical procedures under spinal anesthesia. Dosage and method of administration are described subsequently. The age of the patients ranged from 14 to 91 years. Anesthesia was induced with procaine, pontocaine, nupercaine, Intracaine and monocaine. Duration of anesthesia ranged from fifty minutes to six hours and ten minutes. The average duration was approximately three hours inasmuch as nupercaine was used in the majority of the cases. Distribution of sensory anesthesia was below the tenth thoracic segment in 16 per cent, the eleventh to seventh thoracic segment in 64 per cent and above the seventh thoracic segment in 20 per cent of the cases. Fifty-three per cent of the subjects were males and 47 per cent were females. In 40 per cent of the cases, the oenethyl was given prophylactically to avoid an anticipated hypotension. In the remaining cases, the drug was given therapeutically to combat hypotension when it appeared. Age, color, sex, risk, premedication, physical findings, and so forth, were recorded along with blood pressure and respiration. Blood pressure was recorded at two to

five minute intervals until it became stabilized. In the first 100 cases blood pressure determinations were taken at one hour intervals for six hours after the operation was completed. The appearance of untoward signs and symptoms such as tachycardia, palpitation, tremor, pallor, sweating, apprehension, dilatation of the pupil and other systemic effects suggestive of sympathetic stimulation were carefully noted.

RESULTS

On the whole, oenethyl proved to be an effective vasopressor and successfully combated the hypotension of spinal anesthesia in the majority of the patients to whom it was administered. In 2.5 per cent of the cases it failed to cause an elevation in blood pressure. However, in these cases, ephedrine and other vasopressors likewise were ineffective. In 5 per cent of the cases the response was slow and the drug failed to restore the blood pressure to the preoperative level. The average effective therapeutic dose necessary to restore a fallen pressure varied between 75 mg. to 100 mg. intramuscularly. The intramuscular route was satisfactory only if the systolic pressure was not below 90 mm. of mercury. In a number of instances, doses of 100 mg. were in excess of the required amount and more than the desired elevation. When used prophylactically, likewise, 75 to 100 mg. intramuscularly also appeared to be the effective dose. When the circulatory depression was severe or appeared precipitously, intravenous administration was the safest and most satisfactory route. Best results were obtained by administering the drug in divided doses of 5 to 10 mg. each and allowing one-quarter to one-half minute to elapse between the administration of each fraction. Under such circumstances, the blood pressure was observed continuously to avoid overdosage. On the average, 25 mg. was sufficient to produce the desired effect. In cases in which the systolic pressure had fallen to dangerous levels (50–60 mm.), as much as 50 mg. intravenously was often necessary to restore the blood pressure to the preoperative level. Rapid administration of an estimated dose in a single injection is frequently followed by too pronounced a rise in blood pressure. Overdosage not only causes an excessive rise in blood pressure but also a temporary disturbance in cardiac rhythm. Results obtained by using the drug by the continuous drip method are disappointing.

When administered intravenously, the elevation in blood pressure was established within one to two minutes. When administered intramuscularly, the onset of action was delayed somewhat compared to the response obtained by intravenous use, but appeared within two to three minutes in the majority of patients. On certain occasions, as long as five minutes elapsed before a rise occurred. The more pronounced the drop in pressure, the greater the dose and the longer the time interval necessary for the pressor effect to appear. The vasopres-

sor effect was maximal within ten minutes as a rule. When the drug was given in divided doses intravenously until the preanesthetic systolic level was attained, the pressure continued to rise for five minutes or more and tended to exceed the preanesthetic level. Although the pressor effect following one single injection was sustained for the duration of the operation in the majority of cases, it was frequently necessary to repeat the dose when the drug was first used. As a rule, repetition was necessary in older subjects or in those in whom "high" spinal anesthesia was employed. In the last 300 administrations, a combined technic was instituted. Twenty-five milligrams was given intravenously. This was followed by 50 mg. intramuscularly after the pressor effect was established. By employing the technic of doubling the intravenous dose necessary to elicit the pressor effect and giving it intramuscularly, the pressor effect was sustained and repetition was unnecessary. The "follow-up" blood pressure for six hours after administration revealed no depression of the circulation following the stimulation.

Oenethyl caused an elevation in systolic, diastolic and pulse pressures after spinal anesthesia had been induced. Apparently there is a difference in the behavior of the amine in anesthetized and unanesthetized subjects. Attempts to elevate the blood pressure over normal levels in unanesthetized subjects have been disappointing unless large doses were employed (7). However, no attempted comparative studies were made in this series and this point requires further study and clarification. The average rise in systolic pressure varied with the circumstances. Although attempts were made to gage the dose so that the systolic pressure was restored to the preanesthetic level, this was rarely accomplished save in a small percentage of the cases. An increase in systolic pressure ranging from 20 to 60 mm. of mercury over the postanesthetic level was obtained. A rise in diastolic pressure, which as a rule was proportional to the rise in systolic pressure, was likewise observed. In this respect, this vasopressor differs from epinephrine and ephedrine. The former causes a lowering of diastolic pressure; the latter as a rule produces little or no change from the preanesthetic values.

Restoration of venous pressure to the preanesthetic level following the depression caused by spinal anesthesia was noted in 6 subjects upon whom suitable observations were made. Although no conclusion can be drawn from so few observations, these results suggest that the drug has a constricting action upon the venous circulation.

The pulse rate was not significantly altered, although in approximately 6 per cent of the patients an increase over the preanesthetic level occurred soon after the drug was administered. In the majority of subjects, it varied little from the preoperative rate unless trauma, hemorrhage or other effects of the surgical procedure caused it to change. As there appeared to be no apparent cause for the increase,

the change was ascribed to the drug. Tachycardia, however, was seldom observed. An increase in pulse rate was most frequent in subjects who developed the bradycardia which on occasions accompanies spinal anesthesia. The greatest increase in pulse rate noted was approximately 20 per minute. This effect upon pulse differs from that of epinephrine and ephedrine which usually cause a notable increase in pulse rate. This action upon pulse rate is more like that observed when neosynephrine is employed. None of the patients receiving the drug complained of palpitation. No difference in pulse rate was noted between the intravenous and intramuscular use of the drug.

Disturbances in rhythm ascribable to the drug were not observed except when overdosage caused the blood pressure to soar to excessive heights. The majority of disturbances in rhythm appeared to be extra systoles. Electrocardiographic studies were not performed on any of these subjects, however. Cyclopropane, ethylene and ether were necessary as supplemental anesthetics in approximately 5 per cent of the cases. Disturbances in rhythm were not observed when oenethyl had preceded the induction of inhalation anesthesia.

The rate and amplitude of respirations were increased in approximately 15 per cent of the patients receiving the drug. This stimulating action on respiration occurred most frequently in cases in which the drug had been administered prophylactically rather than in those requiring it therapeutically. The mechanism producing this stimulation is undetermined.

Pupillary dilatation, though of little clinical significance, was observed in approximately 15 per cent of the patients. When it appeared, it persisted for approximately thirty minutes. It occurred especially in patients receiving the upper dose range (100 mg.). Transitory dizziness shortly after the administration of the drug occurred in 10 per cent of the cases. Nausea and emesis occurred in 5 per cent of the subjects anesthetized. It is possible that the hypotension of spinal anesthesia or traction upon the abdominal organs, rather than the effect of the oenethyl, produces these responses. Pallor of varying degree appeared in over half of the subjects. Inasmuch as pallor usually accompanies circulatory depression, it is difficult to ascribe its appearance to the effects of the drug. When pallor was observed, it was usually accompanied by moistness of the skin. Profuse sweating was not observed in any case.

The drug is not recommended to overcome hypotension due to shock from operative trauma, hemorrhage or other causes not directly related to spinal anesthesia itself. Hypotension caused by spinal anesthesia usually appears immediately or shortly after motor and sensory anesthesia is established. Presumably it is neurogenic in origin and results from a disparity between the vascular space and blood volume. This disparity is caused by an increase in size of that portion of the vascular bed composed of the arterioles, capillaries and venules. The

blood volume is little altered at first in spinal anesthesia. Vasopressors correct this disparity and restore the circulation to nearly normal. Changes in blood volume which occur as the operation progresses are best controlled by administration of fluid. In many cases, vasopressors are harmful.

CONCLUSION

Oenethyl, or 2-methylaminoheptane, is an aliphatic secondary saturated amine which possesses a vasopressor action. The drug was administered to overcome the hypotension from spinal anesthesia in 1,000 operative cases. Side actions such as nervousness, palpitation, headache, dizziness, sweating and so forth were not common. The substance appears to be a satisfactory vasopressor for spinal anesthesia and is worthy of further clinical trial.

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MEETING OF THE AMERICAN SOCIETY FOR THE ADVANCEMENT OF GENERAL ANESTHESIA IN DENTISTRY

The Spring Meeting will be held at the Hotel New Yorker, 34th Street and 8th Avenue, New York City, on Monday, March 25, 1946, at 8:15 p.m. A pre-meeting dinner will be held at the Hotel at 7:00 p.m.

The speaker will be Lt. Col. Stevens J. Martin, Tilton General Hospital, Fort Dix, N. J., who will speak on "The Physiology of Respiration with Special Reference to Anesthesia." Dr. Martin was formerly Assistant Professor of Physiology at the Albany Medical College, Albany, N. Y.

The Profession is cordially welcome.